Janssen Vaccines & Prevention B.V.

Clinical Protocol

A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate the Safety and Immunogenicity of Seasonal Influenza Vaccine and Ad26.RSV.preF, with and without Co-administration, in Adults Aged 60 Years and Older in Stable Health

Protocol VAC18193RSV2003; Phase 2a
Amendment 2

VAC18193 (JNJ-64400141)

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

Status: Approved
Date: 6 December 2017
Prepared by: Janssen Vaccines & Prevention B.V.
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

Protocol History VAC18193RSV2003		
Document Type and *File Name*	Issued Date	Comments
Initial Clinical Trial Protocol *VAC18193RSV2003_Protocol (v1)*	03-September-2017	-
Protocol Amendment 1 *VAC18193RSV2003_Protocol_Amend_1*	15-November-2017	For details, please refer to Section Amendment 1
Protocol Amendment 2 *VAC18193RSV2003_Protocol_Amend_2*	This document	For details, please refer to Section Amendment 2

TABLE OF CONTENTS

LIST OF ATTACHMENTS

LIST OF IN-TEXT TABLES AND FIGURES

TABLES

FIGURES

PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	03 September 2017
Amendment 1	15 November 2017
Amendment 2	06 December 2017

Amendments below are listed beginning with the most recent amendment.

Amendment 2 (06 December 2017)

The overall reason for the amendment:
This amendment is made to correct an error in the description of placebo vial size.

The table below gives an overview of the rationale for each change and all affected sections

Rationale: To correct an error in the description of placebo vial size: vial size for placebo was corrected to 2 mL.

14.1 Physical Description of Study Vaccine

Amendment 1 (Issued date: 15 November 2017)

The overall reason for the amendment:
This amendment is made to clarify procedures for handling nasal turbinate samples, to specify immunogenicity criteria for subjects to be offered revaccination after Day 57, to allow subjects on medication for chronic underlying illness to participate if the dose is either stable or has not undergone clinically significant changes for at least 12 weeks, and to allow subjects with only a childhood history of eczema to participate.

The table below gives an overview of the rationale for each change and all affected sections

Rationale: To clarify if subjects experience signs and symptoms of an RTI, nasal turbinate samples should be stored refrigerated at home and brought to the site within 3 to 4 days. Alternatively, subjects may go to the site within 1-2 days of the start of the RTI to have nasal turbinate samples taken by study staff.

Synopsis
Time and Events Schedule
9.2.3 Signs and Symptoms of RTI

Rationale: To allow vital signs measurements to be taken in a sitting position as well as supine.

Time and Events Schedule
9.1.3 Screening and First Vaccination (Day 1)
9.2.2.3 Vital Signs

Rationale: To clarify that nasal turbinate sample kits will be distributed with the RTI forms.

Time and Events Schedule

Rationale: To clarify that, if the dose of any medication at screening has not been stable for at least 12 weeks, subjects may still be enrolled if only small, clinically non-significant changes have been made in the judgement of the PI.

4.1 Inclusion Criteria

Rationale: To clarify that subjects with only a childhood history of eczema are allowed to participate.

4.2 Exclusion Criteria

Rationale: To specify additional immunogenicity criteria for subjects to be offered revaccination after Day 57.
11.6 Planned Analyses
Rationale: To align the protocol-specified AE severity criteria for AEs not listed in the FDA toxicity tables in Attachment 1 with the FDA severity criteria.
12.1.3 Severity Criteria
Rationale: To amend the description of the Ad26.RSV.preF vaccine.
14.1 Physical Description of Study Vaccine
Rationale: Other minor changes and corrections made throughout the protocol.

SYNOPSIS

A Randomized, Double-blind, Placebo-controlled Phase 2a Study to Evaluate the Safety and Immunogenicity of Seasonal Influenza Vaccine and Ad26.RSV.preF, with and without Co-administration, in Adults Aged 60 Years and Older in Stable Health

- Ad26.RSV.preF (JNJ-64400141), a replication-incompetent adenovirus serotype 26 (Ad26) containing a deoxyribonucleic acid (DNA) transgene that encodes for the pre-fusion conformation-stabilized F protein (pre-F) derived from the respiratory syncytial virus (RSV) A2 strain.

RATIONALE

Influenza and respiratory syncytial viruses cause infection leading to seasonal illness, hospitalization, morbidity and mortality in the elderly. Influenza vaccines are given yearly before the start of the influenza season and it is likely that an RSV vaccine would be given at the same time, as both RSV and influenza seasons overlap. This study will examine the effect on the safety and immunogenicity of both vaccines of giving a seasonal influenza vaccine and Ad26.RSV.preF at the same time and at separate times to provide an indication of whether these vaccines can be used concomitantly.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Primary Objectives

- To demonstrate the non-inferiority of the concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine versus the administration of seasonal influenza vaccine alone in terms of humoral immune response expressed by the geometric mean titers (GMTs) of hemagglutination inhibition (HI) antibody titers against all four influenza vaccine strains 28 days after the administration of influenza vaccine, using a non-inferiority margin of 2 for the GMT ratio (control group/co-administration group)
- To assess the safety and tolerability of a single dose of $1x10^{11}$ viral particles (vp) of Ad26.RSV.preF, administered intramuscularly to subjects aged ≥60 years separately or concomitantly with seasonal influenza vaccine

Secondary Objectives

- To compare the safety of seasonal influenza vaccine administered separately and concomitantly with Ad26.RSV.preF
- To assess humoral immune responses to RSV after the administration of Ad26.RSV.preF administered separately or concomitantly with seasonal influenza vaccine
- To assess humoral immune responses to influenza after the administration of seasonal influenza vaccine administered separately or concomitantly with Ad26.RSV.preF, in terms of geometric mean fold rises from baseline of HI antibody titers against the four influenza vaccine strains
- Seroconversion rates against the four influenza vaccine strains defined as a post-vaccination titer ≥1:40 in subjects with a pre-vaccination titer of <1:10, or a ≥4-fold titer increase in subjects with a pre-vaccination titer of ≥1:10
- Seroprotection rates against the four influenza vaccine strains defined as the percentage of subjects with a post-vaccination titer ≥1:40

Exploratory Objectives

- To explore the comparison between seasonal influenza vaccine administered separately and concomitantly with Ad26.RSV.preF in terms of cellular responses to RSV F protein (by enzyme-linked immunospot [ELISpot] assay, flow cytometry) in a limited number of subjects, if feasible
- To explore the comparison between seasonal influenza vaccine administered separately and concomitantly with Ad26.RSV.preF in terms of other immunologic responses to RSV
- To monitor symptoms of respiratory illness via the respiratory tract infection (RTI) symptoms form from Day 1 through the end of the study

Primary Endpoints

- HI titers against all four influenza vaccine strains
- Safety and tolerability of Ad26.RSV.preF

  Solicited local and systemic adverse events (AEs) for 7 days after each vaccination

  Unsolicited AEs from informed consent form (ICF) signature until 28 days after the second vaccination

  Serious adverse events (SAEs) from ICF signature throughout the study

Secondary Endpoints

- Safety and tolerability of seasonal influenza vaccine

  Solicited local and systemic AEs for 7 days after the first vaccination

  Unsolicited AEs from ICF signature until 28 days after the first vaccination

  SAEs from ICF signature throughout the study
- Immunogenicity

  The analysis of the immunogenicity of the Ad26.RSV.preF and seasonal influenza vaccine will include the characterization of humoral responses.

  Humoral Immune Response

  - RSV neutralization A2 strain

    Analysis of RSV A2 neutralizing titers of the vaccine-induced immune response will be assessed
  - RSV F-protein enzyme-linked immunosorbent assay (ELISA; pre- and/or post-fusion F antibodies)

    Analysis of antibodies binding to RSV F protein in post-fusion and pre-fusion form
  - Hemagglutination inhibition assay (HAI)

    Analysis of HI to all the influenza vaccine strains included in the seasonal vaccination

Exploratory Endpoints

- Immunogenicity

  Additional exploratory analyses may be performed to investigate vaccine-elicited immune responses further. These may include, but are not limited to, the following assays:

  Humoral Immune Response

  - RSV cross-neutralization of B and/or other A strain
  - F-protein antibody specificity characterization
  - Adenovirus neutralization assay
  - Functional and molecular antibody characterization
  - Influenza virus neutralization assay

  Cell-mediated Immune Response to Ad26.RSV.preF and Seasonal Influenza Vaccine

  - IFNγ ELISpot cytokine analysis
  - Intracellular cytokine staining

Hypothesis

To demonstrate the non-inferiority of the concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine versus the administration of seasonal influenza vaccine, 28 days after the administration of the seasonal influenza vaccine in terms of humoral immune response, the following hypothesis will be tested for each one of the four influenza vaccine strains:

Null Hypothesis:

- The GMT of HI antibody titers against one vaccine strain, 28 days after concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine is inferior by at least 2 to the GMT 28 days after the administration of seasonal influenza vaccine

Alternative Hypothesis:

- The GMT of HI antibody titers against one vaccine strain, 28 days after concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine is non-inferior to the GMT 28 days after the administration of seasonal influenza vaccine, using a non-inferiority margin of 2, for the ratio $GMT_{\text{control group}}/GMT_{\text{co-administration group}}$

No formal statistical testing of safety data is planned. All safety data will be analyzed descriptively by regimen.

OVERVIEW OF STUDY DESIGN

This is a single center, randomized, placebo-controlled, double-blind Phase 2a study, to be conducted in 180 adult male and female subjects aged ≥60 years of age in stable health randomized in parallel in a 1:1 ratio to one of two groups. Group 1 will receive $1x10^{11}$ vp Ad26.RSV.preF on Day 1 administered at the same time as a commercially available seasonal influenza vaccine, and placebo on Day 29. Group 2 will receive placebo on Day 1, administered at the same time as a commercially available seasonal influenza vaccine, and $1x10^{11}$ vp Ad26.RSV.preF on Day 29. All study vaccines will be given by the intramuscular route. An internal data review committee (DRC) will be commissioned for this study.

Table 1: Study Design

Group	N	Day 1	Day 29
1	90	Ad26.RSV.preF ($1x10^{11}$ vp) + Fluarix	Placebo
2	90	Placebo + Fluarix	Ad26.RSV.preF ($1x10^{11}$ vp)

N = number of subjects; vp = viral particles

After each vaccination, subjects will be closely observed for a minimum of 30 minutes post-vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs will be documented by study-site personnel following this observation period. Subjects will be given a thermometer, ruler and daily assessment (subject) diary with instructions for the proper recording of events. Each subject will record solicited local (at injection site) and systemic AEs and body temperatures, beginning on the evening of each study vaccine dosing day and on a daily basis for the following 7 days. Body temperatures should be taken at approximately the same time each day. Study-site personnel will collect and review subject diary information and confirm the entries at subsequent site visits.

Unsolicited AEs will be collected from ICF signature through 28 days after the second vaccination. SAEs will be collected from ICF signature until the end of the study. All AEs, including any that are ongoing 28 days after the second vaccination, will be followed until clinical resolution or stabilization. Concomitant medications will be collected and recorded in the electronic case report form (eCRF) from the time of first vaccination through 28 days after the second vaccination, and additionally outside of this period when associated with an SAE.

Blood will be collected from all subjects to assess humoral immune responses pre-vaccination on each dosing day, and at 28 days after the second vaccination (or at the early exit visit if the subject prematurely terminates the study before Day 57 without withdrawing consent[a]); cellular immune responses may be assessed at these timepoints in a subset containing 40 randomized subjects (ie, 20 per group).

An independent unblinded statistician and unblinded biomarker representative will present data to the DRC if non-inferiority of the concomitant administration of influenza vaccine with Ad26.RSV.preF versus the administration of influenza vaccine alone is not demonstrated, based on the immunogenicity analysis at 28 days after the first dose. The DRC will decide if subjects should be offered repeat influenza immunization (see the Planned Analyses section for more details).

The study duration will be approximately 30 weeks per participant. The study comprises vaccination for each subject on Day 1 and Day 29, a 28-day follow-up period after each vaccination, and a follow-up until 6 months after the second vaccination. The end of the study will be the last subject's last visit by telephone at 6 months after the second vaccination.

Procedures in the Event of an RTI

Signs and symptoms of RTI will be recorded from Day 1 through the end of the study using a specific RTI Symptoms Form. The RTI Symptoms Form will be the primary source for RTI monitoring. Subjects should complete a new form each day they experience symptoms, including the day on which symptoms resolve. Subjects will be contacted periodically during the study to remind them to complete the RTI Symptoms Form in the event of any symptoms of RTI and to contact the site at the time of symptom onset. Completed RTI forms can either be mailed to the site or brought to the site at the next visit.

If respiratory symptoms develop, the following should take place:

[a] Immunogenicity blood samples will only be taken if early exit is at least 14 days after the previous immunogenicity blood draw.

- Subjects should contact the site
- Subjects should record signs and symptoms of the RTI (including measurement of oral body temperature) daily using the RTI Symptoms Form until the day of symptom resolution
- If feasible, subjects should take a nasal turbinate sample at home. Alternatively, subjects may go to the site within 1-2 days of the start of the RTI to have nasal turbinate samples taken by study staff.

Nasal turbinate samples will be stored refrigerated at home and brought to the site within the next 3 to 4 days. The presence of RSV infection will be assessed by the sponsor by reverse transcriptase polymerase chain reaction (RT-PCR) diagnostics on the nasal turbinate samples.

Blood from any subject with a suspected RTI may be assayed by a serological assay (eg, protein G and/or N ELISA) to confirm RSV infection. *Note*: No additional blood sampling is necessary – any serological assay conducted to confirm RSV infection will use blood from the existing samples. Signs and symptoms of RTIs will also be reported as unsolicited AEs if they occur between first vaccination and 28 days following the second vaccination; any RTI fulfilling the criteria of an SAE would be reported as such during the entire study period.

SUBJECT POPULATION

Subjects will be adult men and women, aged ≥60 years on the day of signing the ICF. All subjects will be in good or stable health (on the basis of physical examination, medical history, 12-lead electrocardiogram (ECG) and vital signs measurement performed on Day 1).

DOSAGE AND ADMINISTRATION

On Day 1 and Day 29, each subject will receive separate intramuscular injections of Ad26.RSV.preF or placebo, and of a seasonal influenza vaccine, according to the schedule shown in Table 1.

- Ad26.RSV.preF (JNJ-64400141): will be supplied at a concentration of $2x10^{11}$ vp/1.0 mL in single-use vials (0.5 mL extractable volume). A dose level of $1x10^{11}$ vp will be used
- Fluarix® Quadrivalent (suspension for intramuscular injection): 2017/18 season influenza vaccine
- Placebo (saline solution)

For each subject, each injection will be 0.5 mL in volume. On Day 1, subjects will receive two intramuscular injections, one in each arm; on Day 29, subjects will receive one intramuscular injection. The right arm should be used for seasonal influenza vaccination doses on Day 1; the left arm should be used for Ad26.RSV.preF/placebo doses on Days 1 and 29.

An unblinded pharmacist, or other qualified individual, who will have no other study function will prepare the appropriate vials and syringes, labeled with the subject's identification number, and provide the syringes for Ad26.RSV.preF and placebo in a blinded manner to the blinded study vaccine administrator (ie, blinded for Ad26.RSV.preF; Fluarix administration will not be blinded) who will perform the injection.

Full details of study vaccine preparation will be provided in the Site Investigational Product Procedures Manual.

IMMUNOGENICITY EVALUATIONS

Humoral and cellular immunogenicity evaluations are summarized in the tables below. Sample collection and processing will be performed by the staff at the clinical site according to current versions of approved standard operating procedures. Humoral immune responses will be assessed in all subjects; cellular immune responses may be assessed in a subset containing 40 randomized subjects (ie, 20 per group).

Table 2: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Primary endpoints	
HAI	Hemagglutination inhibition assay to influenza vaccine strains
Secondary endpoints	
RSV neutralization A2	Analysis of neutralizing antibodies to the A2 strain
F-protein antibody (ELISA; pre- and/or post-fusion)	Analysis of antibodies binding to RSV F protein in post-fusion and/or pre-fusion form
HAI	Hemagglutination inhibition assay to influenza vaccine strains
Exploratory endpoints	
RSV strain cross-neutralization	Analysis of cross-neutralizing antibodies to B and/or a different A strain
F-protein antibody specificity characterization	Analysis of RSV, pre-fusion and post-conformation specific antibodies, antibody binding to pre-F or post-F after adsorption with pre-F or post-F proteins, and epitope mapping
Adenovirus neutralization	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including ADCC, ADCP, avidity, Fc characteristics, Ig isotype

ADCC = antibody-dependent cell-mediated cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; ELISA = enzyme-linked immunosorbent assay; F = fusion; HAI = hemagglutination inhibition assay; Ig = immunoglobulin; RSV = respiratory syncytial virus

Table 3: Summary of Immunogenicity Assays (Cellular)

Assay	Purpose
Exploratory endpoints	
IFNγ ELISpot	T-cell responses to RSV F-protein peptides and/or influenza proteins/peptides
Flow cytometry (ICS)	Analysis of T-cell responses to RSV F-protein peptides and/or influenza protein peptides (including, but not limited to, CD4/CD8, IL2, IFNγ, TNFα and/or activation markers, memory, Th1/Th2 subtyping)

ELISpot = enzyme-linked immunospot; F = fusion; IFNγ = interferon gamma; ICS = intracellular cytokine staining; IL = interleukin; Th = T-helper (cell); RSV = respiratory syncytial virus; TNFα = tumor necrosis factor alpha

SAFETY EVALUATIONS

On a daily basis, for 7 days after each vaccination, subjects will be asked to record the following AEs via the subject diary:

- Solicited local AEs at the Ad26.RSV.preF (or placebo) and seasonal influenza vaccine injection sites: erythema (measured using the ruler supplied), swelling/induration (measured using the ruler supplied, and graded using the functional scale), and pain/tenderness.
- Solicited systemic AEs: fatigue, headache, myalgia, arthralgia, chills, nausea and fever (ie, body temperature ≥38 °C).

Body temperature should be measured at approximately the same time each day, preferably in the evening, using the thermometer supplied (oral route preferred).

The investigator will review each subject's diary at the subsequent site visit; diary information will be transcribed by the study personnel into the eCRF.

The investigator or study-site staff will document any reported unsolicited AEs and perform causality evaluations from the time of ICF signature through 28 days after the second vaccination. SAEs will be collected from the time of ICF signature until the study end, 6 months after the second vaccination.

Subjects will record signs and symptoms of RTIs using the RTI Symptoms Form: signs and symptoms of RTIs will be collected on the RTI Symptoms page in the eCRF. RTIs, preferably as a diagnosis, will also

be reported on the AE page of the eCRF if they occur from between first vaccination and 28 days following the second vaccination.

STATISTICAL METHODS

Sample Size Determination[a]

As four seasonal influenza strains will be assessed for which non-inferiority is to be shown, 94.6% power is required for each individual seasonal influenza strain to ensure an overall power of at least 80%. To have 94.6% power for an individual influenza strain, 86 evaluable subjects/group are required. If approximately 5% subjects are unevaluable (due to dropout, missing data, or seasonal influenza), 90 randomized subjects/arm will be needed.

This sample size ensures at least 80% power, assuming statistical independence between the HI antibody titers for the four seasonal influenza strains. As some correlation between the responses to the four strains is likely, the actual overall power may be higher.

Planned Analyses

- **28 days post-first dose immunogenicity analysis**: at 28 days post-first dose, an immunogenicity analysis will be performed by an independent unblinded statistician. The goal of this analysis will be to evaluate the non-inferiority of the concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine versus the administration of seasonal influenza vaccine alone in terms of the humoral immune response expressed by the GMTs of HI antibody titers against the four influenza vaccine strains. The independent unblinded statistician and unblinded biomarker representative will present data to the DRC if non-inferiority of concomitant versus separate administration is not demonstrated. The DRC will decide if subjects should be offered repeat influenza immunization after Day 57.
- **Primary analysis:** 28 days post-second dose safety and immunogenicity analysis. This analysis will be performed based on unblinded data. The goal of this analysis will be to evaluate the primary objectives. The blind will be maintained at the subject/site level.
- **Final analysis:** 6 months post-second dose safety analysis. This analysis will be performed based on unblinded data. The goal of this analysis will be to assess safety.

Immunogenicity Analyses

The primary immunogenicity objective will be assessed by calculating the 95% one-sided upper confidence limit for the difference in log-transformed HI antibody titers for each of the four seasonal influenza vaccine strains between control and co-administration groups. The confidence limit will be calculated using Welch's t-interval method. The confidence limit will be back-transformed (by exponentiation) to a GMT ratio and compared to the non-inferiority limit of 2.

Only if the 95% one-sided upper confidence limit for the GMT ratio (Control group/Co-administration group) of the HI antibody titers lies below 2 for each of the four vaccine strains, non-inferiority of co-administration versus separate administration will be concluded. If one or more confidence limits for the GMT ratio exceed 2, non-inferiority cannot be concluded.

As a sensitivity analysis, the primary endpoint will also be evaluated adjusting for baseline HI levels.

[a] Sample size calculation assumes: (a) immune response is measured by HI antibody titers against the four influenza vaccine strains; (b) a standard deviation of 2 at the $\log_2$ scale for HI antibody titers

Continuous secondary and exploratory variables will be summarized with descriptive statistics of the actual values and the changes from baseline where appropriate. Descriptive statistics (geometric mean and 95% confidence interval for ELISA, virus neutralization and HI assays; median and quartiles for ELISpot and intracellular cytokine staining [ICS]) will be calculated for continuous immunologic parameters at all timepoints. For the humoral assays, geometric mean fold rises from baseline and corresponding 95% confidence intervals might additionally be calculated. For immunogenicity, baseline is considered as the last assessment pre-vaccination. Graphical representations of immunologic parameters will be made as applicable.

Safety Analyses

No formal statistical testing of safety data is planned. For the planned analyses, safety data will be analyzed descriptively by regimen.

TIME AND EVENTS SCHEDULE

Clinic Visit #	1	2 [a] ☎	3	4 [a] ☎	5	6 [b] ☎	Exit [c]
Visit Timing	**Vac 1**	**Vac 1 + 7 d**	**Vac 2**	**Vac 2 + 7 d**	**Vac 2 + 28 d**	**Vac 2 + 6 mo**	
Visit Day	**1**	**8**	**29**	**36**	**57**	**211**	
Visit Window		**±2 d**	**±3 d**	**±2 d**	**±3 d**	**±14 d**	
Visit Type	Screening and **VACCINATION 1**	Safety	**VACCINATION 2**	Safety	Safety and Immuno.	Safety	Early exit
Written informed consent [d]	❶						
Inclusion/exclusion criteria	❶						
Demographics	❶						
Medical history/pre-study meds	❶						
Physical examination [e]	❶		❶		●		●
Vital signs [f] incl. body temperature	❷		❷		●		●
12-lead ECG [g]	❶						
Randomization	❶						
Inclusion/exclusion criteria check [h]			❶				
Pre-vaccination symptoms [i]	❶		❶				
Cellular immunity, mL [j]	❶ 40		❶ 40		40		❸ 40
Humoral immunity, mL [j]	❶ 20		❶ 20		20		❸ 20
Vaccination	●		●				
30 minute post-vaccination observation [k]	●		●				
Solicited AE recording	- - - - - - ❹ - - - - - -		- - - - - - ❹ - - - - - -				❺
Unsolicited AE recording	- - - - - - - - - - - - - - - *continuous* - - - - - - - - - - - - - -						❻
SAE recording	- - - - - - - - - - - - - - - - - - - *continuous* - - - - - - - - - - - - - - - - - - -						●
Concomitant medications [l]	- - - - - - - - - - - - - - - - - - - *continuous* - - - - - - - - - - - - - - - - - - -						●
RTI [m]	●	- - - - - - - - - - - - - - - *continuous* - - - - - - - - - - - - - - -					●
RTI Symptoms Form and nasal turbinate sample kit distribution [n]	●						
Subject diary distribution [o]	●		●				
Subject diary review by site staff [p]			●		●		
Approximate daily blood draw, mL (*subjects with cellular draw*)	60	–	60	–	60	–	60
Approx. cumulative blood draw, mL (*subjects with cellular draw*)	60	60	120	120	180	**180**	60

Clinic Visit #	1	2 [a] ☎	3	4 [a] ☎	5	6 [b] ☎	Exit [c]
Visit Timing	**Vac 1**	**Vac 1 + 7 d**	**Vac 2**	**Vac 2 + 7 d**	**Vac 2 + 28 d**	**Vac 2 + 6 mo**	
Visit Day	**1**	**8**	**29**	**36**	**57**	**211**	
Visit Window		**±2 d**	**±3 d**	**±2 d**	**±3 d**	**±14 d**	
Visit Type	Screening and **VACCINATION 1**	Safety	**VACCINATION 2**	Safety	Safety and Immuno.	Safety	Early exit
Approximate daily blood draw, mL (*subjects without cellular draw*)	20	–	20	–	20	–	20
Approx. cumulative blood draw, mL (*subjects, without cellular draw*)	20	20	40	40	60	**60**	–

❶ pre-dose; ❷ pre- and post-dose; ❸ blood samples for immunogenicity will only be taken if the early exit is at least 14 days after the previous immunogenicity blood draw; ❹ solicited local and systemic AEs will be collected via subject diaries from vaccination until 7 days after each vaccination; ❺ if within 7 days of the previous vaccination; ❻ if within 28 days of the previous vaccination

a. Safety visits at 7 days after each vaccination will be by telephone.
b. The final visit will be a telephone call to check for any SAEs and associated concomitant medications.
c. For those subjects who are unable to continue participation in the study up to Day 57, but for whom consent is not withdrawn, an exit visit will be conducted as soon as possible.
d. Signing of the ICF should be done before any study-related activity.
e. A full physical examination, including height and body weight, will be carried out on Day 1. At all other visits, an abbreviated, symptom-directed examination will be performed if determined necessary by the investigator.
f. Supine or sitting systolic and diastolic blood pressure, heart rate and respiratory rate after at least 5 minutes rest.
g. Supine ECG after at least 5 minutes rest.
h. To include Inclusion Criteria 3, 4 and 5 and Exclusion Criteria 1, 2 and 15.
i. Investigator must check for acute illness or body temperature ≥38.0 °C at the time of vaccination. In such cases, the subject may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator.
j. Humoral immune responses will be assessed in all subjects; cellular immune responses may be assessed in a subset containing 40 randomized subjects (ie, 20 per group).
k. Subjects will be closely observed for a minimum of 30 minutes post-vaccination. Any unsolicited, solicited local and systemic AEs, and vital signs (supine or sitting systolic and diastolic blood pressure, heart rate respiratory rate and body temperature) will be documented by study-site personnel following this observation period.
l. Concomitant medications will be collected from the time of first vaccination, through 28 days after the second vaccination, and additionally outside of these periods when associated with any SAE. Pre-study therapies administered up to 30 days before first dose of study vaccine will be recorded on Day 1.
m. Signs and symptoms of RTI will be recorded from Day 1 through the end of the study using the specific RTI Symptoms Form.
n. Subjects will be contacted periodically during the study to remind them to complete the RTI Symptoms Form in the event of any symptoms of RTI, to contact the site at the time of symptom onset, and, if feasible, to take a nasal turbinate sample at home. Nasal turbinate samples will be stored refrigerated at home and brought to the site within 3 to 4 days. Alternatively, subjects may go to the site within 1-2 days of the start of the RTI to have nasal turbinate samples taken by study staff.
o. Rulers and thermometers will be distributed at Visits 1 and 3.
p. Subjects will be contacted by telephone 2 to 4 days after the first and second vaccinations, to remind them to fill in the subject diaries and to check that they are entering information correctly.

AE = adverse event; d = day; ECG = electrocardiogram; HIV = human immunodeficiency virus; ICF = informed consent form; mo = month; RSV = respiratory syncytial virus; RTI = respiratory tract infection; SAE = serious adverse event; vac = vaccination

ABBREVIATIONS

Ad26	adenovirus serotype 26
Ad35	adenovirus serotype 35
AE	adverse event
CS	circumsporozoite
DNA	deoxyribonucleic acid
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunospot (assay)
ERD	enhanced respiratory disease
F protein	fusion protein
FA	full analysis (set)
FDA	(US) Food and Drug Administration
FI	formalin-inactivated
FIH	first-in-human
GCP	Good Clinical Practice
GMT	geometric mean titer
HAI	hemagglutination inhibition assay
HI	hemagglutination inhibition
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	intracellular cytokine staining
IEC	Independent Ethics Committee
IFNγ	interferon gamma
Ig	immunoglobulin
IRB	Institutional Review Board
PBMC	peripheral blood mononuclear cell
PI	principal investigator
PPII	per-protocol influenza immunogenicity (set)
PPRI	per-protocol RSV immunogenicity (set)
PQC	Product Quality Complaint
RSV	respiratory syncytial virus
RTI	respiratory tract infection
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SRP	study responsible physician
SUSAR	suspected unexpected serious adverse reaction
US	United States
vp	viral particles

1. INTRODUCTION

A human adenovirus-vectored vaccine candidate which has shown promise in preclinical animal models of respiratory syncytial virus (RSV) will be assessed in this study:

- Ad26.RSV.preF (JNJ-64400141), a replication-incompetent adenovirus serotype 26 (Ad26) containing a deoxyribonucleic acid (DNA) transgene that encodes for the pre-fusion conformation-stabilized F protein (pre-F) derived from the RSV A2 strain.

For the most comprehensive nonclinical information regarding Ad26.RSV.preF, refer to the latest version of the Investigator's Brochure for Ad26.RSV.preF.[1]

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

Background

RSV is an important cause of serious respiratory infections in the elderly, immunocompromised, and those with underlying chronic cardiopulmonary conditions.[9] Although most adults mount a long-lasting fully protective immune response, waning immune responses in the elderly might contribute to increased susceptibility to severe disease after RSV infection causing significant morbidity and mortality. In long-term care facilities, RSV is estimated to infect 5 to 10% of the residents per year with significant rates of pneumonia (10% to 20%) and death (2% to 5%).[10] In an epidemiology study of RSV burden, it was estimated that 11,000 elderly persons die annually of RSV in the United States (US).[28] These data support the importance of developing an effective vaccine for certain adult populations, such as the elderly.

RSV is also considered to be the most important cause of serious acute respiratory illness in infants and children under 5 years of age: worldwide in 2005, RSV caused an estimated 33.8 million new episodes of acute lower respiratory tract infections this age range, with 3.4 million cases requiring hospitalization due to severe illness.[14,26,27]

Despite the high disease burden, no licensed vaccine is available for RSV. The first vaccine candidate for young children, which consisted of formalin-inactivated RSV (FI-RSV), was associated with enhanced respiratory disease (ERD) upon infection with RSV.[15] Although the mechanisms for ERD are not fully understood, it is thought that FI-RSV failed to induce adequate neutralizing antibody titers and CD8 priming, and induced a T-helper 2 (Th2) skewed response.[22]

As all adults have been exposed to RSV, and therefore previously primed by a live virus infection, enhanced disease is not expected to be a concern in this study.[6]

Adenoviral-vectored Vaccines

It is thought that an efficacious RSV vaccine should induce high levels of neutralizing antibodies, $CD8^+$ T-cell responses, and Th1-type $CD4^+$ T cells.[3] The candidate RSV vaccine being evaluated in this protocol is based on the AdVac® platform which has been shown to promote a strong antibody response, as well as $CD8^+$ T cell and Th1-type $CD4^+$ T-cell responses.

The immunogenicity profile of adenoviral vectors, with particular emphasis on Th1 responses, is illustrated by data obtained from immunization of adults with Ad26-vectored human immunodeficiency virus (HIV) vaccine (Ad26.ENVA.01), and of adults and infants with Ad35-vectored tuberculosis (TB) vaccine (Ad35.TB-S). These data show predominantly interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα) production in $CD4^+$ and $CD8^+$ T cells.[2,5,24] Furthermore, in mice, Ad26- and Ad35-vectored vaccines with circumsporozoite (CS) transgene inserts (Ad26.CS.01 and Ad35.CS.01), when administered as single immunizations or in combination as a heterologous prime-boost regimen at dose levels ranging from 1×10^8 vp (viral particles) to 1×10^{10} vp, induce predominantly $CD8^+$ T-cell responses, as well as mainly immunoglobulin IgG2a antibody responses, indicative of a Th1-biased response.[25]

Ad26.RSV.FA2 Clinical Data

Ad26 encoding for the wild-type RSV FA2 transgene, Ad26.RSV.FA2, has been evaluated in studies VAC18192RSV1001 and VAC18192RSV1003 (N = 48 and 32, respectively, of which 35 and 24 subjects, respectively, received Ad26.RSV.FA2) in adults at doses of 5×10^{10} vp. All subject visits have been completed in both studies.

Results indicate that there have been no safety concerns following vaccination in either study. After vaccination with Ad26.RSV.FA2, local reactogenicity comprised almost exclusively mild to moderate pain of median duration 1 to 3 days. The most commonly experienced solicited systemic adverse events (AEs; headache, fatigue, chills, myalgia) were also mostly mild to moderate and of median duration 1 to 3 days; most unsolicited AEs and most laboratory abnormalities were mild to moderate in severity. No serious adverse events (SAEs) were reported and no AEs led to withdrawal from study vaccine.[31]

Single vaccination with 5×10^{10} vp Ad26.RSV.FA2 raised humoral and cellular immunity. An increase in RSV neutralizing antibody titers was observed; RSV-specific T-cell responses were also increased.

FA2 and preF RSV Vaccines

The candidate vaccine assessed in this study is Ad26.RSV.preF, ie, a replication-incompetent Ad26 containing a DNA transgene that encodes for the pre-fusion conformation-stabilized F protein derived from the RSV A2 strain.

First-in-human clinical studies (VAC18192RSV1001 [first-in-human (FIH) for Ad35.RSV.FA2] and VAC18192RSV1003 [FIH for Ad26.RSV.FA2]) have been completed with vaccines

Ad26.RSV.FA2 and Ad35.RSV.FA2, in which Ad26 and Ad35, respectively, encode for a wild-type RSV F protein of the RSV A2 strain (FA2).

The F protein of RSV undergoes a conformational transition from a metastable pre-fusion conformation to a stable post-fusion conformation. Neutralizing sensitive epitopes reside on both proteins, but recent evidence indicates that those epitopes specific to the pre-F protein seem to be more potent than those present on the post-F protein.[12,13] This evidence resulted in the design of the candidate RSV vaccine (Ad26.RSV.preF) in which the adenoviral vector encodes for a full length RSV F protein stabilized in the pre-F protein conformation. CCI [redacted] This change in the transgene confers more stability to the pre-fusion form of the molecule before it undergoes its natural transition to the post-fusion form.[18] This change also induces higher immune responses against pre-fusion epitopes because the majority of neutralizing antibodies target the pre-fusion protein conformation.[19,23] For these reasons, it is anticipated that the Ad26.RSV.preF vaccine candidate will generate more neutralizing antibodies relative to the Ad26.RSV.FA2 vaccine.[31]

Ad26.RSV.preF Preclinical Data

Preclinical studies were performed in naïve and RSV pre-exposed animals. Ad26.RSV.preF is immunogenic in mice and cotton rats, with humoral responses that include the induction of RSV neutralizing antibodies. In addition, Ad26.RSV.preF was shown to elicit cellular responses in mice, characterized by the induction of RSV F-specific CD8+ IFNγ+ T cells. Single immunization with Ad26.RSV.preF protects cotton rats from challenge with RSV A2 and RSV B strains.[31]

Ad26.RSV.preF Clinical Data

Ad26.RSV.preF is under evaluation in the ongoing FIH Phase 1 study VAC18193RSV1003 in subjects aged ≥60 years in stable health. In this randomized, placebo-controlled, double-blind study, 72 male and female subjects were randomized in parallel to 1 of 5 study groups and have received the first (Day 1) of 2 intramuscular injections as follows:

- Group 1 – 5×10^{10} vp Ad26.RSV.preF on Day 1 and 1 year (± 1 month) later;
- Group 2 – 5×10^{10} vp Ad26.RSV.preF on Day 1 and placebo 1 year (± 1 month) later;
- Group 3 – 1×10^{11} vp Ad26.RSV.preF on Day 1 and 1 year (± 1 month) later;
- Group 4 – 1×10^{11} vp Ad26.RSV.preF on Day 1 and placebo 1 year (± 1 month) later;
- Group 5 – placebo on Day 1 and 1 year (± 1 month) later.

Safety and immunogenicity data from the unblinded interim analysis 28 days post-Dose 1 from all 72 subjects who received Ad26.RSV.preF (5×10^{10} vp or 1×10^{11} vp) or placebo confirmed the immunogenicity of the vaccine; the 1×10^{11} vp dose of Ad26.RSV.preF was more immunogenic than the 5×10^{10} vp dose. No safety concerns were revealed; the reactogenicity of both doses was comparable.

For study VAC18193RSV1003, Ad26.RSV.preF was provided in a different buffer (Formulation Buffer 1[a]) from the one to be used in the current study (Formulation Buffer 2[b]). The formulation buffer was changed to enhance the Ad26.RSV.preF drug product stability at 2 to 8 °C for storage purposes in future studies. The new formulation buffer was considered well-tolerated when tested in a nonclinical single dose intramuscular safety study in rabbits.[31]

Safety Data Supporting Ad26.RSV.preF Dose Selection from Other Ad26-based Vaccines

In addition to the 2 completed studies with Ad26.RSV.FA2 and 1 ongoing study with Ad26.RSV.preF, the dose levels for Ad26.RSV.preF used in this study are supported by experience in adults with other Ad26 vaccines encoding for different antigens (EnvA [in Ad26.ENVA.01 against HIV];[4,5] CS protein [in Ad26.CS.01 against malaria];[7,24] and Ebola glycoprotein [in Ad26.ZEBOV against Ebola virus][21]). Note that, in general, at a given dose level, no significant changes in the safety profiles of Ad26-based vaccines have been seen when the transgene has been changed.

In completed clinical studies, the safety of Ad26.ENVA.01, Ad26.CS.01 and Ad26.RSV.FA2 has previously been evaluated in at least 293 adult subjects, of whom 243 have received 5×10^{10} vp, and found to be well-tolerated. In addition, four Phase 1 studies with Ad26.ZEBOV have been completed in adults: 291 subjects have received Ad26.ZEBOV at 5×10^{10} vp and 1×10^{11} vp without significant safety issues: 15 subjects have received 1×10^{11} vp (25 doses administered), and 276 subjects have received 5×10^{10} vp. The safety data from these Ebola studies showed no safety concerns at 5×10^{10} vp and 1×10^{11} vp. Overall, these clinical data are supportive of dosing Ad26.RSV.preF at 1×10^{11} vp in the current study.

1.2. Seasonal Influenza Vaccine

Fluarix® Quadrivalent (GlaxoSmithKline) is a seasonal, split virion influenza vaccine containing four strains of influenza viruses with 15 µg HA/strain per 0.5 mL dose propagated in embryonated chicken eggs. Fluarix is indicated for active immunization against influenza caused by the specific strains of influenza virus contained in the vaccine in adults and children 3 years of age and older. The vaccine is usually administered intramuscularly by injection into the deltoid muscle.

1.3. Overall Rationale for the Study

Influenza and respiratory syncytial viruses cause infection leading to seasonal illness, hospitalization, morbidity and mortality in the elderly. Influenza vaccines are given yearly before the start of the influenza season and it is likely that an RSV vaccine would be given at the same time, as both RSV and influenza seasons overlap. This study will examine the effect on the safety and immunogenicity of both vaccines of giving a seasonal influenza vaccine and

a CCI

b

Ad26.RSV.preF at the same time and at separate times to provide an indication of whether these vaccines can be used concomitantly.

Further discussion on the rationale for the study design is provided in Section 3.2.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Objectives

Primary Objectives

- To demonstrate the non-inferiority of the concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine versus the administration of seasonal influenza vaccine alone in terms of humoral immune response expressed by the geometric mean titers (GMTs) of hemagglutination inhibition (HI) antibody titers against all four influenza vaccine strains 28 days after the administration of influenza vaccine, using a non-inferiority margin of 2 for the GMT ratio (control group/co-administration group)
- To assess the safety and tolerability of a single dose of $1x10^{11}$ vp of Ad26.RSV.preF, administered intramuscularly to subjects aged ≥60 years separately or concomitantly with seasonal influenza vaccine

Secondary Objectives

- To compare the safety of seasonal influenza vaccine administered separately and concomitantly with Ad26.RSV.preF
- To assess humoral immune responses to RSV after the administration of Ad26.RSV.preF administered separately or concomitantly with seasonal influenza vaccine
- To assess humoral immune responses to influenza after the administration of seasonal influenza vaccine administered separately or concomitantly with Ad26.RSV.preF, in terms of geometric mean fold rises from baseline of HI antibody titers against the four influenza vaccine strains
- Seroconversion rates against the four influenza vaccine strains defined as a post-vaccination titer ≥1:40 in subjects with a pre-vaccination titer of <1:10, or a ≥4-fold titer increase in subjects with a pre-vaccination titer of ≥1:10
- Seroprotection rates against the four influenza vaccine strains defined as the percentage of subjects with a post-vaccination titer ≥1:40

Exploratory Objectives

- To explore the comparison between seasonal influenza vaccine administered separately and concomitantly with Ad26.RSV.preF in terms of cellular responses to RSV F protein (by

enzyme-linked immunospot [ELISpot] assay, flow cytometry) in a limited number of subjects, if feasible

- To explore the comparison between seasonal influenza vaccine administered separately and concomitantly with Ad26.RSV.preF in terms of other immunologic responses to RSV
- To monitor symptoms of respiratory illness via the respiratory tract infection (RTI) symptoms form from Day 1 through the end of the study

2.1.2. Endpoints

Primary Endpoints

- HI titers against all four influenza vaccine strains
- Safety and tolerability of Ad26.RSV.preF

  Solicited local and systemic AEs for 7 days after each vaccination

  Unsolicited AEs from informed consent form (ICF) signature until 28 days after the second vaccination

  SAEs from ICF signature throughout the study

Secondary Endpoints

- Safety and tolerability of seasonal influenza vaccine

  Solicited local and systemic AEs for 7 days after the first vaccination

  Unsolicited AEs from ICF signature until 28 days after the first vaccination

  SAEs from ICF signature throughout the study

- Immunogenicity

  The analysis of the immunogenicity of the Ad26.RSV.preF and seasonal influenza vaccine will include the characterization of humoral responses.

  Humoral Immune Response

  - RSV neutralization A2 strain

    Analysis of RSV A2 neutralizing titers of the vaccine-induced immune response will be assessed

  - RSV F-protein enzyme-linked immunosorbent assay (ELISA; pre- and/or post-fusion F antibodies)

    Analysis of antibodies binding to RSV F protein in post-fusion and pre-fusion form

  - Hemagglutination inhibition assay (HAI)

    Analysis of HI to all the influenza vaccine strains included in the seasonal vaccination

Exploratory Endpoints

- Immunogenicity

  Additional exploratory analyses may be performed to investigate vaccine-elicited immune responses further. These may include, but are not limited to, the following assays:

  Humoral Immune Response

  - RSV cross-neutralization of B and/or other A strain
  - F-protein antibody specificity characterization
  - Adenovirus neutralization assay
  - Functional and molecular antibody characterization
  - Influenza virus neutralization assay

  Cell-mediated Immune Response to Ad26.RSV.preF and Seasonal Influenza Vaccine

  - IFNγ ELISpot cytokine analysis
  - Intracellular cytokine staining

Refer to Section 9.2 for evaluations related to endpoints.

2.2. Hypothesis

To demonstrate the non-inferiority of the concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine versus the administration of seasonal influenza vaccine, 28 days after the administration of the seasonal influenza vaccine in terms of humoral immune response, the following hypothesis will be tested for each one of the four influenza vaccine strains:

Null Hypothesis:

- The GMT of HI antibody titers against one vaccine strain, 28 days after concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine is inferior by at least 2 to the GMT 28 days after the administration of seasonal influenza vaccine

Alternative Hypothesis:

- The GMT of HI antibody titers against one vaccine strain, 28 days after concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine is non-inferior to the GMT 28 days after the administration of seasonal influenza vaccine, using a non-inferiority margin of 2, for the ratio $GMT_{\text{control group}}/GMT_{\text{co-administration group}}$

No formal statistical testing of safety data is planned. All safety data will be analyzed descriptively by regimen.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a single center, randomized, placebo-controlled, double-blind Phase 2a study, to be conducted in 180 adult male and female subjects aged ≥60 years of age in stable health randomized in parallel in a 1:1 ratio to one of two groups. Group 1 will receive $1x10^{11}$ vp Ad26.RSV.preF on Day 1 administered at the same time as a commercially available seasonal influenza vaccine, and placebo on Day 29. Group 2 will receive placebo on Day 1, administered at the same time as a commercially available seasonal influenza vaccine, and $1x10^{11}$ vp Ad26.RSV.preF on Day 29. All study vaccines will be given by the intramuscular route. An internal data review committee (DRC) will be commissioned for this study.

Table 4: Study Design

Group	N	Day 1	Day 29
1	90	Ad26.RSV.preF ($1x10^{11}$ vp) + Fluarix	Placebo
2	90	Placebo + Fluarix	Ad26.RSV.preF ($1x10^{11}$ vp)

N = number of subjects; vp = viral particles

After each vaccination, subjects will be closely observed for a minimum of 30 minutes post-vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs will be documented by study-site personnel following this observation period. Subjects will be given a thermometer, ruler and daily assessment (subject) diary with instructions for the proper recording of events. Each subject will record solicited local (at injection site) and systemic AEs and body temperatures, beginning on the evening of each study vaccine dosing day and on a daily basis for the following 7 days. Body temperatures should be taken at approximately the same time each day. Study-site personnel will collect and review subject diary information and confirm the entries at subsequent site visits.

Unsolicited AEs will be collected from ICF signature through 28 days after the second vaccination. SAEs will be collected from ICF signature until the end of the study. All AEs, including any that are ongoing 28 days after the second vaccination, will be followed until clinical resolution or stabilization. Concomitant medications will be collected and recorded in the electronic case report form (eCRF) from the time of first vaccination through 28 days after the second vaccination, and additionally outside of this period when associated with an SAE.

Blood will be collected from all subjects to assess humoral immune responses pre-vaccination on each dosing day, and at 28 days after the second vaccination (or at the early exit visit if the subject prematurely terminates the study before Day 57 without withdrawing consent[a]); cellular immune responses may be assessed at these timepoints in a subset containing 40 randomized subjects (ie, 20 per group).

[a] Immunogenicity blood samples will only be taken if early exit is at least 14 days after the previous immunogenicity blood draw.

An independent unblinded statistician and unblinded biomarker representative will present data to the DRC if non-inferiority of the concomitant administration of influenza vaccine with Ad26.RSV.preF versus the administration of influenza vaccine alone is not demonstrated, based on the immunogenicity analysis at 28 days after the first dose. The DRC will decide if subjects should be offered repeat influenza immunization (see Section 11.6 for more details).

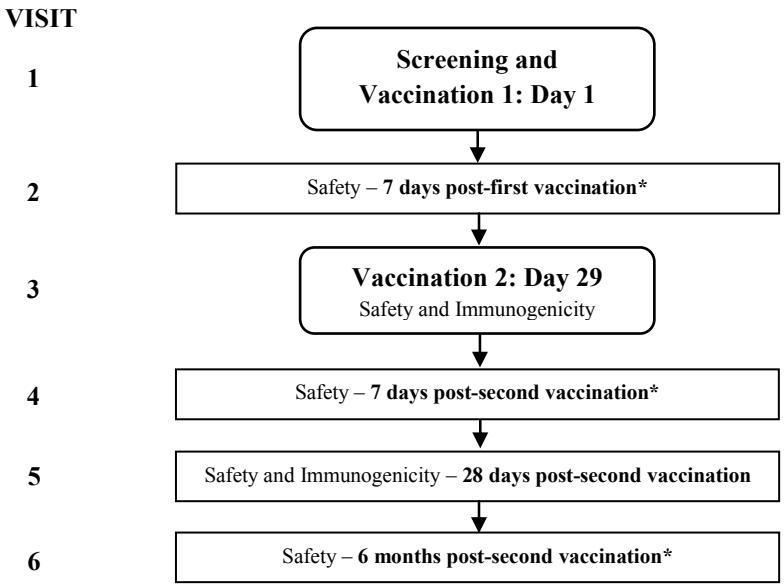
The study duration will be approximately 30 weeks per participant. The study comprises vaccination for each subject on Day 1 and Day 29, a 28-day follow-up period after each vaccination, and a follow-up until 6 months after the second vaccination. The end of the study will be the last subject's last visit by telephone at 6 months after the second vaccination.

If symptoms of an RTI develop from Day 1 through the end of the study, subjects should record signs and symptoms of the RTI using a specific RTI Symptoms Form and, if feasible, take a nasal turbinate sample. Details on procedures in the event of an RTI are described in Section 9.2.3.

Unscheduled study visits may be performed based on investigator's clinical judgment and may include further evaluations, as needed.

A diagram of the entire study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



*by telephone

3.2. Study Design Rationale

Availability of Safety Data Prior to Dosing

Two initial FIH studies (VAC18192RSV1001, N = 48; VAC18192RSV1003, N = 32) in healthy adults examining homologous and heterologous regimens of 5×10^{10} vp of Ad26.RSV.FA2 and 5×10^{10} vp of Ad35.RSV.FA2 have been completed. Both Ad26.RSV.FA2 and Ad35.RSV.FA2 were shown to be safe and immunogenic.

One subsequent FIH study (VAC18193RSV1003, N = 72) in adults aged 60 years and older in stable health examining homologous regimens of 5×10^{10} vp and 1×10^{11} vp of Ad26.RSV.preF is ongoing. All 72 subjects have been randomized and have received the first dose. Safety data from the unblinded interim analysis 28 days post-Dose 1 from all 72 subjects who received Ad26.RSV.preF (5×10^{10} vp or 1×10^{11} vp) or placebo did not reveal any safety concerns.

Dose Selection

The rationale behind selection of the Ad26 vector and dose selection is described in Section 1.1.

Rationale for Vaccine Regimen Selection

Influenza vaccines are given yearly before the start of the season and it is likely that an RSV vaccine would be given at the same time. This study will examine the effect on the immunogenicity of both vaccines of giving a seasonal influenza vaccine and Ad26.RSV.preF at the same time and at separate times to provide an indication of whether these vaccines can be used concomitantly.

Thus, male and female subjects aged ≥60 years will be dosed with $1x10^{11}$ vp Ad26.RSV.preF at the same time as seasonal influenza vaccine on Day 1, and in the absence of seasonal influenza vaccine on Day 29.

4. SUBJECT POPULATION

The inclusion and exclusion criteria for enrolling subjects in this study are described in the following two subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

Screening for eligible subjects will be performed pre-vaccination on Day 1.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Each subject must sign an ICF indicating that he or she understands the purpose of and procedures required for the study, is willing to participate in the study and attend all scheduled visits, and is willing and able to comply with all study procedures and adhere to the prohibitions and restrictions specified in this protocol.
2. Subject must be a man or woman, ≥60 years old on the day of signing the ICF and available for the duration of the study.
3. Before randomization, a woman must be:
   - postmenopausal
     A postmenopausal state is defined as no menses for 12 months without an alternative medical cause; and
   - not intending to conceive by any methods.
4. Criterion modified per Amendment 1:

   4.1 In the investigator's clinical judgment, subject must be either in good or stable health, and not at risk of serious complications from influenza. Subjects may have underlying illnesses such as hypertension, type 2 diabetes, hyperlipoproteinemia, or hypothyroidism, as long as their symptoms/signs are medically controlled. If they are on medication for a condition, the medication dose must have been stable for at least 12 weeks (or only small, clinically non-significant changes have been made in the judgement of the PI) preceding vaccination and expected to remain stable for the duration of the study. Subjects will be included on the basis of physical examination, medical history, vital signs, and 12-lead electrocardiogram (ECG)[a] performed on Day 1.

[a] Retesting of abnormal vital signs or ECG values that may lead to exclusion, or due to equipment malfunction, will be allowed once without prior approval from the sponsor.

5. From the time of first vaccination through 3 months after the second dose of study vaccine, subject agrees not to donate blood.
6. Subject must be willing to provide verifiable identification, have means to be contacted and to contact the investigator during the study.

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

1. Subject has acute illness (this does not include minor illnesses such as diarrhea) or temperature ≥38.0 ºC within 24 hours prior to the first dose of study vaccine; enrollment at a later date is permitted.
2. Subject has a serious chronic disorder, including severe chronic obstructive pulmonary disease or clinically significant congestive heart failure, requirement for supplemental oxygen, end stage renal disease with or without dialysis, clinically unstable cardiac disease, Alzheimer's disease, or has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise well-being) or that could prevent, limit, or confound the protocol-specified assessments.
3. Subject has history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with minimal risk of recurrence).
4. Subject has had major surgery (per the investigator's judgment), within 4 weeks before dosing, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 6 months after the final dose of study vaccine. *Note*: Subjects with planned surgical procedures to be conducted under local or locoregional anesthesia and not judged as major by the investigator may participate.
5. Subject has chronic active hepatitis B or hepatitis C infection, documented by hepatitis B surface antigen and hepatitis C antibody, respectively.
6. Subject has HIV type 1 or type 2 infection.
7. Subject has had major psychiatric illness and/or drug or alcohol abuse which in the investigator's opinion would compromise the subject's safety and/or compliance with the study procedures.
8. Subject has a known allergy, or history of anaphylaxis or other serious adverse reactions to vaccines or vaccine components (including any of the constituents of the study vaccines).
9. Subjects with a history of allergy to egg protein.
10. Criterion modified per Amendment 1:
    - 10.1 Subject has a history of chronic urticaria (recurrent hives), eczema and/or atopic dermatitis. *Note*: Subjects with a history of eczema only in childhood are allowed.
11. Subject has a history of acute polyneuropathy (eg, Guillain-Barré syndrome).

12. Subject has abnormal function of the immune system resulting from:
    - Clinical conditions (eg, autoimmune disease or immunodeficiency)
    - Chronic (longer than 10 days) or recurrent use of systemic corticosteroids during the study and within 6 months before first administration of study vaccine (*Note*: Ocular, topical or inhaled steroids are allowed)
    - Administration of antineoplastic and immunomodulating agents or radiotherapy during the study and within 6 months before the first administration of study vaccine.
13. Subject has received treatment with immunoglobulins in the 2 months, or blood products in the 4 months before the planned administration of the first dose of study vaccine or has any plans to receive such treatment during the study.
14. Subject is in receipt of, or planning to receive, licensed live attenuated vaccine within 28 days of each study vaccination (ie, before and after); other licensed vaccines (ie, not live: eg, tetanus, hepatitis A, hepatitis B or rabies) should be given at least 14 days before or 14 days after each study vaccination.
15. Subject has received vaccination with seasonal influenza vaccine for the current influenza season in the Northern Hemisphere.
16. Subject has received an investigational drug or used an invasive investigational medical device within 30 days or received an investigational vaccine within 6 months before the planned administration of the first dose of study vaccine or is currently enrolled or plans to participate in another investigational study during the course of this study. *Note: Participation in an observational clinical study (ie, with no intervention) is allowed upon approval of the sponsor.*
17. Subject has a contraindication to intramuscular injections and blood draws, eg, bleeding disorders.
18. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
19. Subject who, in the opinion of the investigator, is unlikely to adhere to the requirements of the study, or are unlikely to complete the full course of vaccination and observation.
20. Subject cannot communicate reliably with the investigator.
21. Subject is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator, or an employee of the sponsor.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 8 regarding prohibited and restricted therapies and vaccines during the study.
2. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (Section 4.1 and Section 4.2, respectively).
3. Vaccination with live attenuated vaccines within 28 days of a study vaccination (ie, before and after) is prohibited. Other vaccines (eg, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before (or at least 14 days after) administration of study vaccine in order to avoid potential confusion of adverse reactions and potential immune interference. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine.

5. STUDY VACCINE ALLOCATION AND BLINDING

Study Vaccine Allocation

If cellular immune responses are evaluated by the site, subjects will be assigned to two strata prior to randomization, depending on their consent to blood sampling for peripheral blood mononuclear cell (PBMC) assessment and the PBMC sampling capability of the site. The first stratum will contain a maximum of 40 subjects from whom PBMC samples will be collected. The second stratum will contain the remaining subjects, to reach the target of a total of 180 subjects in the study: from these subjects no PBMC samples will be collected. After a maximum of 40 subjects has been assigned to the first stratum, the remaining subjects will be assigned to the second stratum regardless of their PBMC sampling consent. Within each stratum, subject will be randomized 1:1 to one of the two groups. The two strata will be randomized in parallel, depending on the PBMC capability of the site.

If cellular immune responses are not evaluated by the site, then subjects will be randomized 1:1 in one of the two groups.

Randomizations will be based on computer-generated schedules prepared before the study by or under the supervision of the sponsor. The randomizations will be balanced by using randomly permuted blocks.

A unique code will dictate the study vaccine assignment for the subject.

Withdrawal of randomized subjects from vaccination before the first dose: If randomized subjects are withdrawn from vaccination before the first dose is administered, additional subjects may be recruited to replace these subjects at the discretion of the sponsor. Any replacement subject will be assigned to the same group as the original (discontinued) subject. The

replacement subject's randomization number will equal the randomization number of the discontinued subject +1000 (for example subject 0001 would be replaced by subject 1001).

Withdrawal of randomized subjects from vaccination after the first dose (for reasons other than due to an AE): Any randomized subject who is withdrawn from the study for reasons other than due to an AE after the first dose but before the second dose might be replaced at the discretion of the sponsor. Any replacement subject will be assigned to the same group as the original (discontinued) subject. The replacement subject's randomization number will equal the randomization number of the discontinued subject +2000.

Blinding

The investigator will be provided with a sealed randomization code for each subject, containing coded details of study vaccine allocation. All randomization codes, whether opened or sealed, will be collected after the end of the subject's participation in the study.

Unblinding[a] will only occur at the time of database lock of the primary analysis. While the responsibility to break the study vaccine allocation code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In such cases, the investigator may in an emergency determine the identity of the study vaccine by opening the sealed code. In the event the blind is broken, the sponsor must be informed as soon as possible. The date, time and reason for the unblinding must be documented in the appropriate section of the eCRF. The investigator is advised not to reveal the study vaccine assignment to the study-site personnel or sponsor personnel.

The subjects, study-site personnel (including the vaccine administrator) and investigator will be blinded to study vaccine allocation throughout the study, except for the pharmacist or qualified staff member with primary responsibility for study vaccine preparation and dispensing. *Note*: Only Ad26.RSV.preF administration will be blinded; Fluarix administration will not be blinded.

If the randomization code is broken by the investigator or the study-site personnel, the subject must discontinue further study vaccine administration and must be followed as appropriate (see Section 10.2 for details). If the randomization code is broken by the sponsor for safety reporting purposes, the subject should not discontinue further study vaccine administration and may remain in the study (if the randomization code is still blinded to the study-site personnel and the subject).

[a] ie, at the subject level.

6. DOSAGE AND ADMINISTRATION

On Day 1 and Day 29, each subject will receive separate intramuscular injections of Ad26.RSV.preF or placebo, and of a seasonal influenza vaccine, according to the schedule shown in Table 4.

- Ad26.RSV.preF (JNJ-64400141): will be supplied at a concentration of $2x10^{11}$ vp/1.0 mL in single-use vials (0.5 mL extractable volume). A dose level of $1x10^{11}$ vp will be used
- Fluarix® Quadrivalent (suspension for intramuscular injection): 2017/18 season influenza vaccine
- Placebo (saline solution)

For each subject, each injection will be 0.5 mL in volume. On Day 1, subjects will receive two intramuscular injections, one in each arm; on Day 29, subjects will receive one intramuscular injection. The right arm should be used for seasonal influenza vaccination doses on Day 1; the left arm should be used for Ad26.RSV.preF/placebo doses on Days 1 and 29.

An unblinded pharmacist, or other qualified individual, who will have no other study function will prepare the appropriate vials and syringes, labeled with the subject's identification number, and provide the syringes for Ad26.RSV.preF and placebo in a blinded manner to the blinded study vaccine administrator (ie, blinded for Ad26.RSV.preF; Fluarix administration will not be blinded) who will perform the injection.

Full details of study vaccine preparation will be provided in the Site Investigational Product Procedures Manual.

7. STUDY VACCINE COMPLIANCE

Study vaccine will be administered intramuscularly by a blinded vaccine administrator (ie, blinded for Ad26.RSV.preF; Fluarix administration will not be blinded) – a trained and qualified study nurse, medical doctor, or otherwise qualified healthcare professional. The date and time of each study vaccine administration will be recorded in the eCRF.

8. PRE-STUDY AND CONCOMITANT THERAPY

Pre-study therapies administered up to 30 days before first dose of study vaccine will be recorded on Day 1.

Concomitant therapies will be collected and recorded in the eCRF from the time of first vaccination through 28 days after the second vaccination, and additionally outside of this period when associated with an SAE meeting the criteria outlined in Section 12.3.2. Information on concomitant use of herbal supplements or vitamins will not be collected.

Use of any experimental medication (including experimental vaccines other than the study vaccine) during the study is not allowed.

Analgesic/antipyretic medications and non-steroidal anti-inflammatory drugs (NSAIDS) may be used post-vaccination only in case of medical need (eg, fever or pain) and their use must be documented. Use of these medications as routine prophylaxis prior to study vaccine administration is discouraged.

Chronic (longer than 10 days) or recurrent use of systemic corticosteroids is prohibited during the study and within 6 months before first administration of study vaccine (*Note*: Ocular, topical or inhaled steroids are allowed). Antineoplastic and immunomodulating agents or radiotherapy are prohibited in the 6 months before the first administration of study vaccine and during the study.

If chronic use of prohibited therapies becomes medically indicated during the course of the study for any subject, the sponsor should be contacted.

Vaccination with live attenuated vaccines within 28 days of a study vaccination (ie, before and after) is prohibited. Other vaccines (eg, tetanus, hepatitis A, hepatitis B, rabies) should be given at least 14 days before (or at least 14 days after) administration of study vaccine in order to avoid potential confusion of adverse reactions and potential immune interference. If a vaccine is indicated in a post-exposure setting (eg, rabies or tetanus), it must take priority over the study vaccine. Prior vaccination with seasonal influenza vaccine for the current influenza season is prohibited.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

Evaluation of the safety/tolerability of the vaccine regimens will include vital signs, physical assessment by study-site personnel, and subject reports on signs and symptoms following vaccinations. Additional visits may be required if, in the investigator's opinion, further clinical evaluation is needed.

Subjects will be provided with a thermometer, ruler and subject diary to measure and record body temperature and solicited local (at the Ad26.RSV.preF [or placebo] and seasonal influenza vaccine injection sites) and systemic events. The diary includes instructions how to capture the data and grading scales to assess severity of the symptoms. Study staff are responsible for providing appropriate training for diary completion to the subject to avoid missing or incorrect data. The subject diary will be reviewed by the study personnel at visits indicated on the Time and Events Schedule.

The Time and Events Schedule summarizes the frequency and timing of safety and immunogenicity measurements applicable to this study.

Over the entire study, the total blood volume to be collected from the 40 subjects from whom samples for cellular immunogenicity may be drawn will be approximately 180 mL. For these subjects, the maximum volume of blood to be drawn at any given visit would be 60 mL.

Over the entire study, the total blood volume to be collected from subjects from whom samples for cellular immunogenicity are not drawn will be approximately 60 mL. For these subjects, the maximum volume of blood to be drawn at any given visit will be 20 mL.

9.1.2. Visit Windows

For the following visits, windows will be allowed as indicated:

VISIT	*Visit Day*	*Window*	*Primary Purpose*
Visit 2	Day 8	± 2 days	7 days post-first vaccination, safety only visit, by telephone
Visit 3	Day 29 (Vac 2)	± 3 days	Second vaccination, safety and immunogenicity
Visit 4	Day 36	± 2 days	7 days post-second vaccination, safety only visit, by telephone
Visit 5	Vac 2 +28 days	± 3 days	28 days post-second vaccination, safety and immunogenicity visit
Visit 6	Vac 2 +6 months	± 14 days	Final visit, safety only visit, 6 months post-second vaccination, by telephone

Note: Subjects will be contacted by telephone 2 to 4 days after the first and second vaccinations, to remind them to fill in the subject diaries and to check they are entering information correctly.

9.1.3. Screening and First Vaccination (Day 1)

Visit 1: Screening/Randomization/Vaccination 1

Only subjects in good or stable health without acute illness or fever and complying with the inclusion and exclusion criteria specified in Section 4 will be included into the study. The investigator will provide detailed information on the study to the subjects and will obtain written informed consent prior to each subject's participation in the study. All the procedures described in the Time and Events Schedule will only take place after written informed consent has been obtained.

The following evaluations will be performed to determine eligibility requirements as specified in the inclusion and exclusion criteria:

- Physical examination including vital signs measurement (respiratory rate, heart rate, supine or sitting systolic and diastolic blood pressure and body temperature) and height and weight
- Demographic information

- Medical history
- Review of pre-study medications
- Review of inclusion/exclusion criteria
- 12-lead ECG

After medical history, physical examination, and ECG have been reviewed for completeness and adherence to inclusion and exclusion criteria, the subject can be deemed eligible for the study and randomized as described in Section 5.

Pre-dose samples for baseline immunogenicity will be collected. Before vaccination, the investigator must check for any symptoms of an acute illness or body temperature ≥38.0 °C. In such a situation, the subject may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator.

Administration of first dose of study vaccines according to Table 4.

Subjects will be closely observed for a minimum of 30 minutes post-vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs and vital signs will be documented in the eCRF by study-site personnel following this observation period.

Subjects will be provided with a subject diary, thermometer, and ruler to measure and record body temperature, solicited local and systemic AEs for 7 days post-vaccination.

RTI Symptoms Forms will be distributed to subjects: subjects should record signs and symptoms of an RTI from Day 1 through the end of the study using the RTI Symptoms Form. At each subsequent visit/telephone call, subjects should be informed that, in the event of any symptoms of RTI, they should fill out the specific RTI Symptoms Form daily until symptom resolution.

9.1.4. Second Vaccination (Day 29)

Visit 3: Vaccination 2

Verification of selected eligibility criteria,[a] abbreviated physical examination (at the discretion of the investigator) and measurement of vital signs will be performed for all subjects pre-vaccination. Pre-dose samples for baseline immunogenicity will be collected. Before vaccination, the investigator must check for any symptoms of an acute illness or body temperature ≥38.0 °C. In such a situation, the subject may be vaccinated up to, and no later than 10 days after the scheduled vaccination, or be withdrawn at the discretion of the investigator.

Administration of second dose of study vaccine according to Table 4.

[a] To include fever and any acute illness that precludes vaccination; also receipt of any routine immunizations.

Subjects will be closely observed for a minimum of 30 minutes post-vaccination to monitor for the development of any acute reactions, or longer if deemed necessary by the investigator. Any unsolicited, solicited local or systemic AEs and vital signs will be documented in the eCRF by study-site personnel following this observation period.

Subjects will be provided with a second subject diary, thermometer, and ruler to measure and record body temperature, solicited local and systemic AEs for 7 days post-vaccination. The subject diary for the first vaccination will be reviewed and collected.

9.1.5. Post-first Vaccination Follow-Up

In addition to the visits detailed below, all subjects will be contacted by telephone 2 to 4 days after the first and second vaccinations, to remind them to fill in the subject diaries and to check that they are entering information correctly.

Visit 2 (7 days post-first vaccination)

Visit 2 at 7 days post-vaccination will be a telephone call to check subject diaries and to collect safety information (solicited and unsolicited AEs, SAEs, concomitant medications, and any RTIs).

9.1.6. Post-second Vaccination Follow-Up

Visit 4 (7 days post-second vaccination)

Visit 4 at 7 days post-vaccination will be a telephone call to check subject diaries and to collect safety information (solicited and unsolicited AEs, SAEs, concomitant medications, and any RTIs).

Post-second vaccination: Visit 5 (28 days post-second vaccination)

Visit 5 at 28 days after the second vaccination will include an abbreviated physical examination (at the discretion of the investigator), vital signs measurement, and recording of any AEs/SAEs, concomitant medications, and RTIs. The second subject diary will be reviewed and collected.

9.1.7. Final Visit – 6 Months after the Second Vaccination

Visit 6, the final visit, will be a telephone call and will include recording of any SAEs, concomitant medications associated with any SAE, and any RTIs.

9.1.8. Early Withdrawal – Early Exit Visit

For those subjects who are unable to continue participation in the study up to Day 57, but who do not withdraw consent, an early exit visit will be conducted as soon as possible. In the event of early withdrawal from the study, all procedures required at the final visit (Section 9.1.7) will be performed. Samples for immunogenicity will only be collected if the early exit is at least 14 days after the previous immunogenicity blood draw.

If the early exit visit occurs within 7 days of the previous vaccination, solicited AEs will be recorded; if the early exit visit occurs within 28 days of the previous vaccination, unsolicited AEs will be recorded.

9.2. Study Evaluations

9.2.1. Immunogenicity

Venous blood samples of approximately 20 mL and 40 mL will be collected for the determination of humoral and cellular responses, respectively, pre-vaccination on each dosing day, as well as 28 days after the second vaccination, or at the early exit visit if the subject prematurely terminates the study, without withdrawing consent. (Blood samples for immunogenicity will only be collected if the early exit is at least 14 days after the previous immunogenicity blood draw). Sample collection and processing will be performed by the staff at the clinical site according to current versions of approved standard operating procedures.

It is assumed that all enrolled subjects will have a pre-existing immune response due to previous RSV exposure as well as influenza-specific responses to one or more strains, either by natural exposure to influenza or by annual influenza vaccination (not including the 2017/18 influenza season).

Humoral and cellular immunogenicity evaluations are summarized in Table 5 and Table 6, respectively. Humoral immune responses will be assessed in all subjects; cellular immune responses may be assessed in a subset containing 40 randomized subjects (ie, 20 per group).

Table 5: Summary of Immunogenicity Assays (Humoral)

Assay	Purpose
Primary endpoints	
HAI	Hemagglutination inhibition assay to influenza vaccine strains
Secondary endpoints	
RSV neutralization A2	Analysis of neutralizing antibodies to the A2 strain
F-protein antibody (ELISA; pre- and/or post-fusion)	Analysis of antibodies binding to RSV F protein in post-fusion and/or pre-fusion form
HAI	Hemagglutination inhibition assay to influenza vaccine strains
Exploratory endpoints	
RSV strain cross-neutralization	Analysis of cross-neutralizing antibodies to B and/or a different A strain
F-protein antibody specificity characterization	Analysis of RSV, pre-fusion and post-conformation specific antibodies, antibody binding to pre-F or post-F after adsorption with pre-F or post-F proteins, and epitope mapping
Adenovirus neutralization	Analysis of neutralizing antibodies to adenovirus
Functional and molecular antibody characterization	Analysis of antibody characteristics including ADCC, ADCP, avidity, Fc characteristics, Ig isotype

ADCC = antibody-dependent cell-mediated cytotoxicity; ADCP = antibody-dependent cellular phagocytosis; ELISA = enzyme-linked immunosorbent assay; F = fusion; HAI = hemagglutination inhibition assay; Ig = immunoglobulin; RSV = respiratory syncytial virus

Table 6: Summary of Immunogenicity Assays (Cellular)

Assay	Purpose
Exploratory endpoints	
IFNγ ELISpot	T-cell responses to RSV F-protein peptides and/or influenza proteins/peptides
Flow cytometry (ICS)	Analysis of T-cell responses to RSV F-protein peptides and/or influenza protein peptides (including, but not limited to, CD4/CD8, IL2, IFNγ, TNFα and/or activation markers, memory, Th1/Th2 subtyping)

ELISpot = enzyme-linked immunospot; F = fusion; IFNγ = interferon gamma; ICS = intracellular cytokine staining; IL = interleukin; Th = T-helper (cell); RSV = respiratory syncytial virus; TNFα = tumor necrosis factor alpha

Instructions for the collection, handling, storage, and shipment of blood samples for immunogenicity assay are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of blood samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

9.2.2. Safety Evaluations

Any clinically relevant changes occurring from ICF signature until 28 days after the second vaccination must be recorded on the eCRF. Any clinically significant abnormalities, including those persisting at the end of the study/early withdrawal, will be followed by the investigator until resolution or until a clinically stable endpoint is reached.

The study will include the evaluations of safety and tolerability outlined in the following sections according to the timepoints provided in the Time and Events Schedule.

9.2.2.1. Adverse Events

Unsolicited AEs will be reported by the subject from ICF signature until 28 days after the second vaccination. Solicited AEs will be reported by the subject for 7 days after each vaccination via the subject diary. AEs will be followed by the investigator as specified in Section 12.3.

For solicited AEs, the following applies:

- **Solicited Adverse Events**

Information related to solicited events, as defined in Section 12, will be recorded by subjects in a diary for 7 days after each vaccination. Each subject will be provided with a diary and instructions on how to complete the diary (Section 9.1.1). There will be a minimum 30-minute post-vaccination assessment of solicited events at the site. Diary information will be transcribed by the study personnel in the appropriate eCRF pages.

Injection Site (Local) Adverse Events

Subjects will be asked to note in the diary occurrences of pain/tenderness, erythema and induration/swelling at the study vaccine injection site (Ad26.RSV.preF [or placebo] and seasonal influenza vaccine) daily for 7 days post-vaccination. The extent (largest diameter) of any erythema, and induration/swelling should be measured (using the ruler supplied) and recorded daily. Induration/swelling should also be graded using the functional scale.

- **Injection Site Pain/Tenderness**

  Injection site pain (eg, stinging, burning) is an unpleasant sensory and emotional experience associated with actual or potential tissue damage and occurring at the immunization site (with or without involvement of surrounding tissue). Injection site tenderness is a painful sensation localized at the injection site upon palpation and/or movement of the limb. Due to subjective nature of the reaction, the severity assessment of pain/tenderness is self-reported (if a subject is unable to provide self-report, other reporters include family member/caregiver or health care provider).[11]

- **Injection Site Erythema**

  Injection site erythema is a redness of the skin caused by dilatation and congestion of the capillaries localized at the injection site. It can best be described by looking and measuring.

- **Injection Site Swelling/Induration**

  Injection site swelling is a visible enlargement of an injected limb. It may be either soft (typically) or firm (less typical). Injection site induration is a palpable thickening, firmness, or hardening of soft tissue, usually has well-demarcated palpable borders, can be visible (raised or sunken compared to surrounding skin), is often 'woody' to touch and has a flat shape. As differentiation between swelling and induration may be difficult without health care professional's assessment, both symptoms have been combined to allow self-assessment by the subjects. Both swelling and induration can best be described by looking and measuring.

Note: Any other injection site events not meeting the above case definitions should be reported separately as unsolicited AEs.[16,17]

Systemic Adverse Events

Subjects will be instructed on how to record daily temperature using a thermometer provided for home use. Subjects should record body temperatures in the diary in the evening of the day of vaccination, and then daily for the next 7 days approximately at the same time each day. If more than one measurement is made on any given day, the highest temperature of that day will be used in the eCRF.

Fever is defined as endogenous elevation of body temperature ≥38° C, as recorded in at least one measurement.[20]

Subjects will also be instructed on how to note daily in the diary for 7 days after each vaccination symptoms of the following events: fatigue, headache, myalgia, arthralgia, chills, nausea and fever.

The severity of these solicited systemic AEs will be graded by the investigator according to the criteria presented in Section 12.1.3.

If a solicited local or systemic AE is not resolved by 7 days after each vaccination, the follow-up will be captured on the diary. The subject will be instructed to record the date of last symptoms and maximum severity in the diary after resolution.

9.2.2.2. Electrocardiogram

Supine 12-lead ECGs will be performed on Day 1 and interpreted locally; ECGs will only be performed thereafter during the study if clinically indicated based on signs and symptoms.

For 30 minutes prior to the ECG, subjects should refrain from meals, hot or cold beverages and strenuous exercise, and should remain in a room with a comfortable temperature. Each ECG should be obtained after the subject has been at rest for at least 5 minutes.

Enrollment of a subject is allowed even with abnormal ECG results as long as the investigator feels that these are not clinically significant and appropriate for the population.

9.2.2.3. Vital Signs

Supine or sitting blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

The following measurements will be performed:

- Heart rate (beats per minutes, bpm), respiratory rate (breaths per minute), systolic blood pressure (mmHg) and diastolic blood pressure (mmHg)
- Body temperature (oral route preferred)

Confirmatory vital signs measurement can be performed if inconsistent with a prior measurement. If any clinically significant changes in vital signs are noted, they will be reported as AEs and followed to resolution, or until reaching a clinically stable endpoint.

9.2.2.4. Physical Examination

A full physical examination, including height and body weight, will be carried out pre-vaccination on Day 1. At all other visits, an abbreviated, symptom-directed examination will be performed by the investigator based on any clinically relevant issues, clinically relevant symptoms and medical history. Symptom-directed physical examination may be repeated if deemed necessary by the investigator.

Physical examinations will be performed by the investigator or appropriately trained delegate. Any abnormalities or changes in severity noted during the review of body systems should be documented in the eCRF.

9.2.3. Signs and Symptoms of RTI

Signs and symptoms of RTI will be recorded from Day 1 through the end of the study using a specific RTI Symptoms Form. The RTI Symptoms Form will be the primary source for RTI

monitoring. Subjects should complete a new form each day they experience symptoms, including the day on which symptoms resolve. Completed RTI forms can either be mailed to the site or brought to the site at the next visit. Subjects will be contacted periodically during the study to remind them to complete the RTI Symptoms Form in the event of any symptoms of RTI and to contact the site at the time of symptom onset.

If respiratory symptoms develop, the following should take place:

- Subjects should contact the site
- Subjects should record signs and symptoms of the RTI (including measurement of oral body temperature) daily using the RTI Symptoms Form until the day of symptom resolution
- If feasible, subjects should take a nasal turbinate sample at home. Alternatively, subjects may go to the site within 1-2 days of the start of the RTI to have nasal turbinate samples taken by study staff.

Nasal turbinate samples will be stored refrigerated at home and brought to the site within the next 3 to 4 days. The presence of RSV infection will be assessed by the sponsor by reverse transcriptase polymerase chain reaction (RT-PCR) diagnostics on the nasal turbinate samples.

Blood from any subject with a suspected RTI may be assayed by a serological assay (eg, protein G and/or N ELISA) to confirm RSV infection. *Note*: No additional blood sampling is necessary – any serological assay conducted to confirm RSV infection will use blood from the existing samples.

Signs and symptoms of RTIs will also be reported as unsolicited AEs if they occur between first vaccination and 28 days following the second vaccination; any RTI fulfilling the criteria of an SAE would be reported as such during the entire study period. Signs and symptoms of RTIs will be collected on the RTI Symptoms page in the eCRF, and also on the AE page in the eCRF if they occur between first vaccination and 28 days following the second vaccination.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY VACCINE/ WITHDRAWAL FROM THE STUDY

10.1. Completion

A subject will be considered to have completed study vaccination if he or she has received both vaccinations on Day 1 and the vaccination on Day 29. A subject will be considered to have completed the study if he or she has completed assessments at the final visit 6 months after the second vaccination.

10.2. Discontinuation of Study Vaccine/Withdrawal from the Study

Discontinuation of Study Vaccine

A subject will not be automatically withdrawn from the study if he or she has to discontinue from study vaccination before the end of the study vaccine regimen.

Subjects will be discontinued from study vaccine administration for the reasons listed below. These subjects must not receive any additional dose of study vaccine but should continue other study procedures, eg, safety follow-up:

- Anaphylactic reaction following vaccination, not attributable to causes other than vaccination
- Any related SAE
- Any related AE, worsening of health status or intercurrent illness that, in the opinion of the investigator, requires study vaccine discontinuation

Withdrawal from the Study

Each subject has the right to withdraw from the study at any time for any reason without affecting the right to treatment by the investigator. Although the subject is not obliged to give a reason for withdrawing prematurely, the investigator should make a reasonable effort to ascertain the reason(s) while fully respecting the subject's rights.

A subject will be withdrawn from the study for any of the following reasons:

- Repeated failure to comply with protocol requirements
- Decision by the sponsor or the investigator to stop or cancel the study
- Decision by local regulatory authorities and Institutional Review Board/Independent Ethics Committee (IRB/IEC) to stop or cancel the study
- Lost to follow-up
- Withdrawal of consent
- Death

Any unnecessary study discontinuation should be avoided. Should a subject be withdrawn, all efforts should be made to complete and report the observations as thoroughly as possible. Whenever a subject is withdrawn from the study, independent of the reason, a final evaluation should be completed for that subject and the major reason for which the subject was withdrawn must be stated. If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/ withdrawal. The measures taken to follow-up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study vaccine assigned to the withdrawn subject may not be assigned to another subject. In general, subjects who withdraw will not be replaced, unless that subject was randomized but did not receive any study vaccine. However, any randomized subject withdrawn from the study for reasons other than due to an AE after the first dose but before the second dose might be replaced at the discretion of the sponsor.

If a subject withdraws early from the study, assessments for early withdrawal should be obtained (see Section 9.1.8).

Subjects who wish to withdraw consent from participation in the study will be offered a single exit visit for safety follow-up (prior to formal withdrawal of consent). They have the right to refuse.

Withdrawal from the Use of Samples in Future Research

The subject may withdraw consent for use of samples for future research (refer to Section 16.2.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF.

10.3. Contraindications to Vaccination

The following events constitute a contraindication to vaccination at that point in time. If any of these events occur at the scheduled time for vaccination, the subject may be vaccinated up to 10 days beyond the scheduled vaccination, or be withdrawn from further vaccination at the discretion of the investigator and after consultation with the sponsor:

- Severe acute illness at the time of vaccination. This does not include minor illnesses such as diarrhea.
- Fever (body temperature ≥38.0 °C) at the time of vaccination.

Note: Other licensed vaccines should be given at least 14 days before or 14 days after study vaccine administration (see Section 4.3).

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the immunogenicity and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

Planned analyses are described in Section 11.6.

The vaccine groups are labeled "CoAd" and "Control" as follows in the remainder of this section:

Group	N	Day 1	Day 29
CoAd	90	Ad26.RSV.preF ($1x10^{11}$ vp) + Fluarix	Placebo
Control	90	Placebo + Fluarix	Ad26.RSV.preF ($1x10^{11}$ vp)

11.1. Analysis Sets

The Full Analysis (FA) Set includes all subjects who were randomized and received at least one dose of study vaccine, regardless of the occurrence of protocol deviations and vaccine type

(seasonal influenza, Ad26.RSV.preF or placebo). Vaccination assignment will follow the as-treated principle. All safety and subject information analyses will be based on the FA set.

The Per-protocol Influenza Immunogenicity (PPII) Set will include all subjects who were randomized and received the first vaccination for whom immunogenicity data are available, excluding subject samples with major protocol deviations expecting to impact the immunogenicity outcomes.

In addition, the following samples will not be included in the PPII set:

- For subjects who experience a seasonal influenza infection (based on RT-PCR, or other sources), samples taken after the natural infection will not be taken into account in the assessment of the immunogenicity of the seasonal influenza vaccine

The analysis of primary immunogenicity endpoint will be based on the PPII set. The analysis of all secondary and exploratory immunogenicity endpoints related to influenza will also be based on the PPII set. Depending on the number of samples excluded, a post-hoc exploratory analysis might be performed, including the excluded samples. To visualize these excluded samples, subject profiles from several assays might be repeated, indicating the excluded samples.

The Per-protocol RSV Immunogenicity (PPRI) Set will include all randomized and fully vaccinated subjects (all three vaccinations, ie, seasonal influenza, Ad26.RSV.preF and placebo) for whom immunogenicity data are available, excluding subject samples with major protocol deviations expecting to impact the immunogenicity outcomes.

In addition, the following samples will not be included in the PPRI set:

- For subjects who experience a natural RSV infection (based on RT-PCR, or other sources), samples taken after the natural infection will not be taken into account in the assessment of the immunogenicity of Ad26.RSV.preF

The analysis of all secondary and exploratory immunogenicity endpoints related to RSV will also be based on the PPRI set. Depending on the number of samples excluded, a post-hoc exploratory analysis might be performed, including the excluded samples. To visualize these excluded samples, subject profiles from several assays might be repeated, indicating the excluded samples.

11.2. Sample Size Determination

Sample size calculations are performed under the following assumptions:

- immune response is measured by HI antibody titers against the four influenza vaccine strains
- a standard deviation of 2 at the $\log_2$ scale for HI antibody titers.

As four seasonal influenza strains will be assessed for which non-inferiority is to be shown, 94.6% power is required for each individual seasonal influenza strain to ensure an overall power of at least 80%. To have 94.6% power for an individual influenza strain, 86 evaluable subjects/group are required. If approximately 5% subjects are unevaluable (due to dropout, missing data, or seasonal influenza), 90 randomized subjects/arm will be needed.

This sample size ensures at least 80% power, assuming statistical independence between the HI antibody titers for the four seasonal influenza strains. As some correlation between the responses to the four strains is likely, the actual overall power may be higher.

11.3. Subject Information

For all subjects, demographic characteristics (eg, age, height, weight, body mass index [BMI], race, and gender), and other baseline characteristics (eg, physical examination, medical history, and concomitant diseases) will be tabulated and summarized with descriptive statistics.

11.4. Immunogenicity Analyses

The **primary immunogenicity objective** is to demonstrate the non-inferiority of the concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine versus the administration of seasonal influenza vaccine alone in terms of humoral immune response expressed by the GMTs of HI antibody titers against all four influenza vaccine strains 28 days after the administration of influenza vaccine, using a non-inferiority margin of 2 for the GMT ratio (Control group/CoAd group).

The primary immunogenicity objective will be assessed by calculating the 95% one-sided upper confidence limit for the difference in log-transformed HI antibody titers for each of the four seasonal influenza vaccine strains between Control and CoAd groups. The confidence limit will be calculated using Welch's t-interval method. The confidence limit will be back-transformed (by exponentiation) to a GMT ratio and compared to the non-inferiority limit of 2.

Only if the 95% one-sided upper confidence limit for the GMT ratio (Control group/CoAd group) of the HI antibody titers lies below 2 for each of the four vaccine strains, non-inferiority of co-administration versus separate administration will be concluded. If one or more confidence limits for the GMT ratio exceed 2, non-inferiority cannot be concluded.

As a sensitivity analysis, the primary endpoint will also be evaluated adjusting for baseline HI levels.

The **secondary and exploratory efficacy endpoints** are listed in Section 2.1.

Continuous secondary and exploratory variables will be summarized with descriptive statistics of the actual values and the changes from baseline where appropriate. Descriptive statistics (geometric mean and 95% confidence interval for ELISA, virus neutralization and HI assays; median and quartiles for ELISpot and intracellular cytokine staining [ICS]) will be calculated for continuous immunologic parameters at all timepoints. For the humoral assays, geometric mean

fold rises from baseline and corresponding 95% confidence intervals might additionally be calculated. For immunogenicity, baseline is considered as the last assessment pre-vaccination. Graphical representations of immunologic parameters will be made as applicable.

No formal non-inferiority assessments for the secondary immunological parameters for seasonal influenza and RSV will be performed, but upper confidence limits for GMT ratios, as described for the primary endpoint, may be calculated and assessed for relevance by comparison to the non-inferiority limit of 2 as used in the primary analysis.

Similarly, the difference in proportions of seroconverted and seroprotected subjects between Control and CoAd groups can be estimated together with the 95% one-sided confidence limit (calculated using Wilson's score method) and compared to a 10% non-inferiority limit. Note that the study is only powered for the four primary comparisons and does not have sufficient power to show non-inferiority of co-administration compared to control for all immunogenicity markers for seasonal influenza and RSV. Consequently, by chance the study may fail to show non-inferiority for one or more secondary endpoints even in the absence of interference between seasonal influenza and RSV vaccine administrations.

For categorical variables, frequency tables will be presented. Difference in proportions and corresponding confidence intervals may be calculated where appropriate.

The primary immunogenicity endpoint will be based on the PPII set. The analysis set for the secondary and exploratory immunogenicity responses related to influenza will be the PPII set, and those related to RSV will be the PPRI. As a sensitivity analysis, key tables may also be based on the FA set. Depending on their occurrence, the effect of natural infections might be further explored.

11.5. Safety Analyses

No formal statistical testing of safety data is planned. All safety data will be analyzed descriptively by regimen.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported AEs with onset during the active phase (ie, AEs occurring after vaccination up to 28 days post-vaccination), and all SAEs will be included in the analysis. For each AE, the number and percentage of subjects who experience at least 1 occurrence of the given event will be summarized by group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue study vaccine due to an AE, or who experience a severe AE or an SAE.

Summaries and/or listings may be provided separately for AEs with onset outside the above defined timeframe (ie, beyond 28 days post-vaccination) and that were reported pre-dose at the moment of subsequent vaccinations for studies using multiple doses.

Solicited local (at the Ad26.RSV.preF [or placebo] and seasonal influenza vaccine injection sites) and systemic AEs will be summarized descriptively. The overall frequencies per vaccine group as well as frequencies according to severity and duration will be calculated for solicited AEs. In addition, the number and percentages of subjects with at least 1 solicited local (at injection site) or systemic AE will be presented. Frequencies of unsolicited AEs, separately for all and vaccination-related only, will be presented by System Organ Class and preferred term.

Vital Signs

A tabulation of the distribution of temperatures per half degree intervals will be provided. For systolic and diastolic blood pressures, pulse rate and respiratory rate, the percentage of subjects with values beyond clinically relevant limits will be summarized.

Electrocardiogram (ECG)

Any abnormalities in ECG parameters (at screening on Day 1) will be listed.

Physical Examination

Physical examination abnormalities will be reported as AEs, according to the investigator.

11.6. Planned Analyses

- **28 days post-first dose immunogenicity analysis:** at 28 days post-first dose, an immunogenicity analysis will be performed by an independent unblinded statistician. The goal of this analysis will be to evaluate the non-inferiority of the concomitant administration of Ad26.RSV.preF and seasonal influenza vaccine versus the administration of seasonal influenza vaccine alone in terms of the humoral immune response expressed by the GMTs of HI antibody titers against the four influenza vaccine strains. The independent unblinded statistician and unblinded biomarker representative will present data to the DRC if non-inferiority of concomitant versus separate administration is not demonstrated. The DRC will decide if subjects should be offered repeat influenza immunization after Day 57. If non-inferiority is not demonstrated but the following criteria[8] are fulfilled, subjects would not be revaccinated:
  - The lower bound of the 95% confidence interval for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 30%
  - The lower bound of the 95% confidence interval for the percentage of subjects achieving an HI antibody titer ≥1:40 should meet or exceed 60%
- **Primary analysis:** 28 days post-second dose safety and immunogenicity analysis. This analysis will be performed based on unblinded data. The goal of this analysis will be to evaluate the primary objectives. The blind will be maintained at the subject/site level.

- **Final analysis:** 6 months post-second dose safety analysis. This analysis will be performed based on unblinded data. The goal of this analysis will be to assess safety.

11.7. Data Review Committee

Data Review Committee

An internal DRC will be commissioned for this study, comprised of sponsor personnel not directly involved in the conduct of the study, who have expertise in clinical study conduct and vaccines. It will consist of at least one medical expert in the relevant therapeutic area and at least one statistician.

The DRC will convene if an effect is seen on immune responses to the seasonal influenza vaccine with concomitant administration based on the immunogenicity analysis at 28 days after the first dose. An independent unblinded statistician and unblinded biomarker representative will present data to the DRC if there is an effect on immune responses to the seasonal influenza vaccine when administered concomitantly with Ad26.RSV.preF. The DRC will decide if subjects should be offered repeat influenza immunization.

The DRC will also convene to discuss any significant or unexpected safety issues. The principal investigator (PI) and study responsible physician (SRP) will inform the DRC of any AE of concern.

After safety reviews, the DRC will make recommendations regarding the continuation of the study. The conclusions of the DRC will be communicated to the investigators, the IRB/IEC and the national regulatory authorities as appropriate. Details will be provided in a separate DRC charter.

If deemed necessary for safety review, the DRC may request the randomization codes and review unblinded data, if applicable.

11.8. Study Vaccination Pausing Rules

The PI and the SRP will monitor the study vaccination pausing rules. If study vaccination is considered to raise significant safety concerns, further vaccination of subjects will be suspended until DRC review is carried out and subsequent communication between the sponsor and the investigator takes place.

The occurrence of any of the following events will lead to suspension of further study vaccination, and trigger a meeting of the DRC to discuss study suspension, adaptation or discontinuation of further vaccination:

1. One or more subjects experience an SAE or other potentially life-threatening (Grade 4) event that is determined to be related to study vaccine; *OR*
2. One or more subjects experience anaphylaxis clearly not attributable to other causes than vaccination with study vaccine; *OR*

3. Two or more subjects experience a Grade 3 or 4 unsolicited AE of the same type, determined to be related to study vaccine, that persists for 72 hours or longer; *OR*
4. Two or more subjects experience a Grade 3 or 4 solicited systemic AE of the same type, determined to be related to study vaccine, that persists for 72 hours or longer; *OR*
5. Death of a subject, regardless of causality.

After the first DRC meeting triggered by the occurrence of a given pausing rule, the DRC will convene thereafter for each additional subject meeting that pausing rule.

The DRC will review blinded safety data first, but is entitled to and has the right to require submission of unblinded data if deemed necessary.

Resumption of vaccinations will start only upon receipt by the study site of written recommendations by the DRC. These communications from the DRC will be forwarded by the investigator to the IRB/IEC and by the sponsor to the relevant health authorities.

To enable prompt response to a situation that would trigger pausing rules 3, 4 or 5, the investigator should update the eCRF with information on any Grade 3 or 4 AE on the same day that the AE is reported.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. For some studies, subjects are not always able to provide valid verbal responses to open-ended questions. In these circumstances, another method of detecting these events is specified.

Solicited Adverse Events

Solicited AEs are pre-defined local (at the Ad26.RSV.preF [or placebo] and seasonal influenza vaccine injection sites) and systemic events for which subjects are specifically questioned and which are noted by subjects in their diary (see Section 9.1.1).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which subjects are specifically not questioned in the subject diary.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with study vaccine. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product (Definition per International Conference on Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects unsolicited AEs starting from ICF signature for 28 days after the second vaccination, and solicited AEs from the time of each vaccination for 7 days post-vaccination (refer to Section 12.3.1 for time of last AE recording). SAEs will be collected from ICF signature for the duration of the study. RTIs, preferably as a diagnosis, will be reported on the AE page of the eCRF if they occur between first vaccination and 28 days following the second vaccination; any RTI fulfilling the criteria of an SAE would be reported as such during the entire study period.

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be

immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between study vaccine and the event (eg, death from anaphylaxis), the event must be reported as a suspected unexpected serious adverse reaction (SUSAR) by the sponsor to health authorities and by the investigator to the IRB/IEC according to regulatory and local requirements.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For Ad26.RSV.preF, the expectedness of an AE will be determined by whether or not it is listed in the Investigator's Brochure.[1]

For Fluarix, the expectedness of an AE will be determined by whether or not it is listed in the package insert.

Adverse Event Associated With the Use of the Vaccine

An AE is considered associated with the use of study vaccine if the attribution is related by the definitions listed in Section 12.1.2.

12.1.2. Attribution Definitions

Every effort should be made by the investigator to explain any AE and assess its potential causal relationship, ie, to administration of study vaccine or to alternative causes (eg, natural history of the underlying diseases, concomitant therapy). This applies to all AEs, whether serious or non-serious.

Causality of AEs should be assessed by the investigator based on the following:

Related: there is suspicion that there is a relationship between study vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that study vaccine contributed to the AE.

Unrelated: there is no suspicion that there is a relationship between study vaccine and the AE; there are other more likely causes and administration of study vaccine is not suspected to have contributed to the AE.

By definition, all solicited AEs at the injection site (local) will be considered related to study vaccine administration.

12.1.3. Severity Criteria

All AEs will be coded for severity using the toxicity grading table in Attachment 1. For AEs not identified in the grading table, the following guidelines will be applied:

Mild (Grade 1): No interference with activity.

Moderate (Grade 2): Some interference with activity not requiring medical intervention.

Severe (Grade 3): Prevents daily activity and requires medical intervention.

Potentially life-threatening (Grade 4): Symptoms causing inability to perform basic self-care functions OR medical or operative intervention indicated to prevent permanent impairment, persistent disability.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

The severity of solicited AEs will be graded in the diary by the subject based on the severity assessment provided in the diary and then verified by the investigator using the FDA toxicity grading table (see Attachment 1).

12.2. Special Reporting Situations

Safety events of interest on a sponsor study vaccine that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Suspected abuse/misuse of a sponsor study vaccine
- Accidental or occupational exposure to a sponsor study vaccine
- Medication error involving a sponsor product (with or without subject/patient exposure to the sponsor study vaccine, eg, name confusion)
- Exposure to a sponsor study vaccine from breast-feeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the Serious Adverse Event page of the eCRF.

12.3. Procedures

12.3.1. All Adverse Events

Unsolicited AEs and special reporting situations will be reported from the time a signed and dated ICF is obtained until 28 days (including relevant visit window, if applicable) after the second vaccination.

Solicited AEs will be recorded by each subject in the subject diary for 7 days after each dosing. The investigator will review each subject's diary at the subsequent site visit; diary information will be transcribed by the study personnel in the on-site assessment forms in the eCRF.

The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

The investigator will monitor and check the study data including all AE data as they become available and will make determinations regarding the severity of the adverse experiences and their relation to study vaccine. All AEs will be deemed related to study vaccine or not related to study vaccine, according to Section 12.1.2.

The investigator must review both post-injection reactogenicity and other AEs to insure the prompt and complete identification of all events that require expedited reporting as SAEs, invoke pausing rules or are other serious and unexpected events.

All AEs, regardless of seriousness, severity, or presumed relationship to study vaccine, must be recorded using medical terminology in the source document and the eCRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the eCRF their opinion concerning the relationship of the AE to study vaccine. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

Each subject will be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number
- Any other information that is required to do an emergency breaking of the blind

12.3.2. Serious Adverse Events

All SAEs occurring from ICF signature until the end of the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form, which must be completed and signed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be made by facsimile (fax).

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than study vaccine or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as an SAE. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or an AE (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the eCRF). *Note*: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered as SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

The cause of death of a subject in a study during the entire study period, whether or not the event is expected or associated with study vaccine, is considered an SAE and must be reported.

12.3.3. Pregnancy

All initial reports of pregnancy in partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form.

Because the effect of study vaccine on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with an SAE, the study-site personnel must report the PQC to the sponsor according to the SAE reporting timelines (refer to Section 12.3.2). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY VACCINE INFORMATION

14.1. Physical Description of Study Vaccine

A human replication-incompetent adenovirus-vectored vaccine candidate, manufactured and provided under the responsibility of the sponsor, will be assessed in this study:

Ad26.RSV.preF (JNJ-64400141)

Ad26.RSV.preF, a replication-incompetent Ad26 containing a DNA transgene that encodes for the pre-fusion conformation-stabilized F protein derived from the RSV A2 strain.

For this study, Ad26.RSV.preF will be formulated as a solution for intramuscular injection. Ad26.RSV.preF will be supplied as a frozen liquid to be thawed prior to use. Ad26.RSV.preF will be filled in stoppered and sealed 2 mL single-use glass vials in a volume of 0.75 mL to allow an extractable volume of at least 0.5 mL (1×10^{11} vp). Refer to the Investigator's Brochure for details of the components of Ad26.RSV.preF and a list of excipients.

Fluarix

Fluarix Quadrivalent: prefilled single dose syringe, 0.5 mL.

Fluarix Quadrivalent is a suspension for intramuscular injection (GlaxoSmithKline) formulated for the 2017/18 season, for active immunization of persons 3 years of age and older for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. The vaccine contains the following four virus strains for 2017/18 northern hemisphere season:

- A/Singapore/GP1908/2015 (H1N1) IVR-180
- A/Hong Kong/4801/2014 (H3N2) NYMC X-263B
- B/Phuket/3073/2013
- B/Brisbane/60/2008

Placebo

Placebo will be supplied as sterile 0.9% saline for injection in 2 mL vials.

14.2. Packaging and Labeling

All study vaccines were manufactured and packaged in accordance with Current Good Manufacturing Practice. All study vaccines will be packaged and labeled under the responsibility of the sponsor. Study vaccine labels will contain information to meet the applicable regulatory requirements.

No study vaccine can be repacked or relabeled without prior approval from the sponsor.

Further details for study vaccine packaging and labeling can be found in the Site Investigational Product Procedures Manual.

14.3. Storage and Handling

Vials must be stored in a secured location under controlled temperature with no access for unauthorized personnel. The study refrigerator/freezer must be equipped with a continuous temperature monitor and alarm. Study refrigerators/freezers should be equipped with back-up

power systems. In the event that study vaccine is exposed to temperatures outside the specified temperature range, all relevant data will be sent to the sponsor to determine if the affected study vaccine can be used or will be replaced. The affected study vaccine must be quarantined and not used until further instruction from the sponsor is received.

Injections should be administered in the deltoid. On Day 1, subjects will receive two intramuscular injections, one in each arm; on Day 29, subjects will receive one intramuscular injection. The right arm should be used for seasonal influenza vaccination doses on Day 1; the left arm should be used for Ad26.RSV.preF/placebo doses on Days 1 and 29. No local or topical anesthetic will be used prior to the injection.

The study vaccine will be prepared by the unblinded site pharmacist, or other qualified individual who will have no other study function and administered by a blinded vaccine administrator.

Further details for study vaccine storage, preparation, handling and stability can be found in the Site Investigational Product Procedures Manual.

14.4. Vaccine Accountability

The investigator is responsible for ensuring that all study vaccine received at the site is inventoried and accounted for throughout the study. The study vaccine administered to the subject must be documented on the vaccine accountability form. All study vaccine will be stored and disposed of according to the sponsor's instructions.

Study vaccine must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study vaccine must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study vaccine will be documented on the vaccine return form. When the study site is an authorized destruction unit and study vaccine supplies are destroyed on-site, this must also be documented on the vaccine return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for vaccine accountability purposes.

Study vaccine should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study vaccine will be supplied only to subjects participating in the study. Study vaccine may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study vaccine from, nor store it at, any site other than the study site agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Investigator's Brochure for Ad26.RSV.preF
- Package Insert for Fluarix
- Site Investigational Product Procedures Manual
- Laboratory Manual
- Electronic Data Capture (eDC) Manual/eCRF completion guidelines and randomization instructions
- Sample ICF
- Subject diary
- Ruler
- Thermometers
- RTI Symptoms Form
- Contact information page(s)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the risks and requirements of the study and, during the study, subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume drawn from each subject will not exceed the US Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP), and FDA guidelines of 550 mL in any eight-week period.[29,30]

Risks Related to Vaccines

Subjects may exhibit local signs and symptoms associated with vaccination, including erythema, swelling/induration, and pain/tenderness. These local reactions will be monitored, but are generally short-term and do not require treatment.

Subjects may exhibit general signs and symptoms associated with administration of a vaccine, or vaccination with placebo, including fatigue, headache, myalgia, arthralgia, chills and nausea. These side effects will be monitored, but are generally short-term and do not require treatment.

Subjects may have an allergic reaction to the vaccination. An allergic reaction may cause a rash, hives or even difficulty breathing. Severe reactions, including anaphylaxis, are rare but can occur

with any vaccine. Medications must be available in the clinic to treat serious allergic reactions promptly.

Risks Related to Adenoviral-vectored Vaccines

Safety data available from 10 completed clinical studies in adults with other Ad26-vectored vaccine candidates, in which Ad26 with different inserts has been evaluated at dose levels ranging from 1×10^{9} vp to 1×10^{11} vp, indicate that no safety concerns would be anticipated from vaccination with Ad26.RSV.preF at doses up to and including 1×10^{11} vp.

Local AEs (moderate injection site pain and tenderness, and moderate to severe redness at the injection site) and systemic AEs (headache, chills, joint pain, muscle pain, tiredness/generally not feeling well/fatigue and fever) have been reported after vaccination with Ad26-vectored vaccines. In a few subjects, transient laboratory abnormalities have been seen, including changes in neutrophils. Laboratory changes including decreased hemoglobin, decreased platelets, and moderate elevations in liver transaminases were observed that were not associated with any clinical findings and appear to be transient based on no reported persistent abnormalities in any of the subjects.

For further details on the safety profiles of other Ad26-vectored vaccine candidates, see the Ad26.RSV.preF Investigator's Brochure.[1]

Risks Related to Fluarix

In adults, the most common (≥10%) local AE after Fluarix Quadrivalent administration was pain (36%); the most common systemic AEs were muscle aches (16%), headache (16%), and fatigue (16%).

Syncope can occur in association with administration of Fluarix Quadrivalent. In the event of syncope, procedures should be in place to avoid falling injury and to restore cerebral perfusion.

For further details, see the Fluarix Package Insert.

Risks from Blood Draws

Blood drawing may cause pain/tenderness, bruising, bleeding, lightheadedness, dizziness, vasovagal response, and, rarely, infection at the site where the blood is taken.

Potential Benefits

There is no direct medical benefit to the subject for participation in this clinical study. Although study subjects may benefit from clinical testing and physical examination, they may receive no direct benefit from participation. Others may benefit from knowledge gained in this study that may aid in the development of an RSV vaccine.

Ad26.RSV.preF is under development for prophylaxis of RSV, however vaccine efficacy has not yet been investigated. There could be a potential benefit from RSV vaccination in terms of

immune response: vaccination could raise an immune response which might confer some additional protection against a future RSV infection.

Vaccination with a seasonal influenza vaccine may provide protection against the influenza A subtype viruses and type B viruses contained in the vaccine.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of

this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study vaccine
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the

reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access. It also denotes that the subject agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand Ad26.RSV.preF, to understand RSV, and to develop tests/assays related to Ad26.RSV.preF and RSV. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw their consent for their samples to be stored for research (refer to Section 10.2).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

17.2.2. Required Pre-study Documentation

The following documents must be provided to the sponsor before shipment of study vaccine to the study site:

- Protocol and amendment(s), if any, signed and dated by the PI.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the PI, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators.
- Documentation of subinvestigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of the current laboratory's normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. In cases where the subject is not randomized into the study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and immunogenicity parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; vaccine receipt/dispensing/return records; study vaccine administration information; and date of study completion and reason for early discontinuation of study vaccine or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The subject diary used to collect information regarding solicited events after vaccination will be considered source data. At Visits 3 and 5, information from the subject diary will be reviewed by the investigator; diary information will be transcribed by study personnel into the eCRF as described in the eCRF Completion Guidelines.

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the eCRF. Any such worksheets will become part of the subject's source documents. Data must be entered into eCRF in English. The eCRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for eCRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review eCRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study-site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The end of the study will be the last subject's last visit 6 after the second vaccination. The study is considered completed with the last visit for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject visit at that study site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study vaccine development

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding Ad26.RSV.preF or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of Ad26.RSV.preF, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per-protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the

study will be used to determine a coordinating investigator. Results of analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multi-center) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multi-center study designs and substudy approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multi-center study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multi-center study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

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31. Data on file.

Attachment 1: Toxicity Tables

Adapted from the FDA Guidance document "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials" (September 2007)

Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to Touch	Discomfort with Movement	Significant discomfort at rest	ER visit or Hospitalization
Erythema/redness*	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever** (°C) Fever** (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	>40 >104
Tachycardia - beats per minute	101 – 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 160	>160	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) - mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate - breaths per minute	17 – 20	21 – 25	>25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 - 100 beats per minute. Use clinical judgment when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or <400 gms/24 hours	4 - 5 stools or 400 - 800 gms/24 hours	6 or more watery stools or >800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Systemic Illness	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-threatening (Grade 4)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study vaccine, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): WOUTER HAAZEN, MD

Institution: Janssen Vaccines & Prevention B.V.

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

LAST PAGE

SIGNATURES

Signed by	Date	Justification
Wouter Haazen	06Dec2017, 11:25:34 AM, UTC	Document Approval